
بسم الله الرحمن الرحيم

*Liver Cirrhosis

Dr . Marwa M. Reda

Asistant professor of internal medicine

Hepatology Unit,

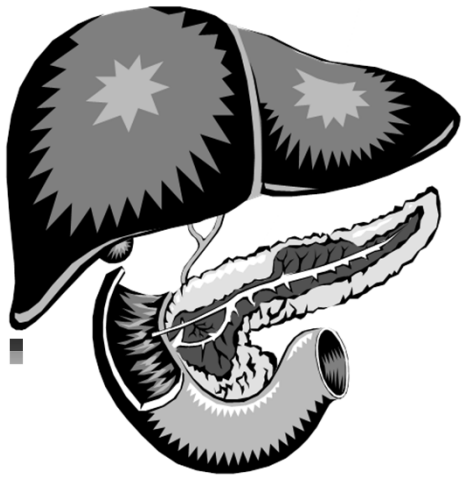
PNU Faculty of Medicine.

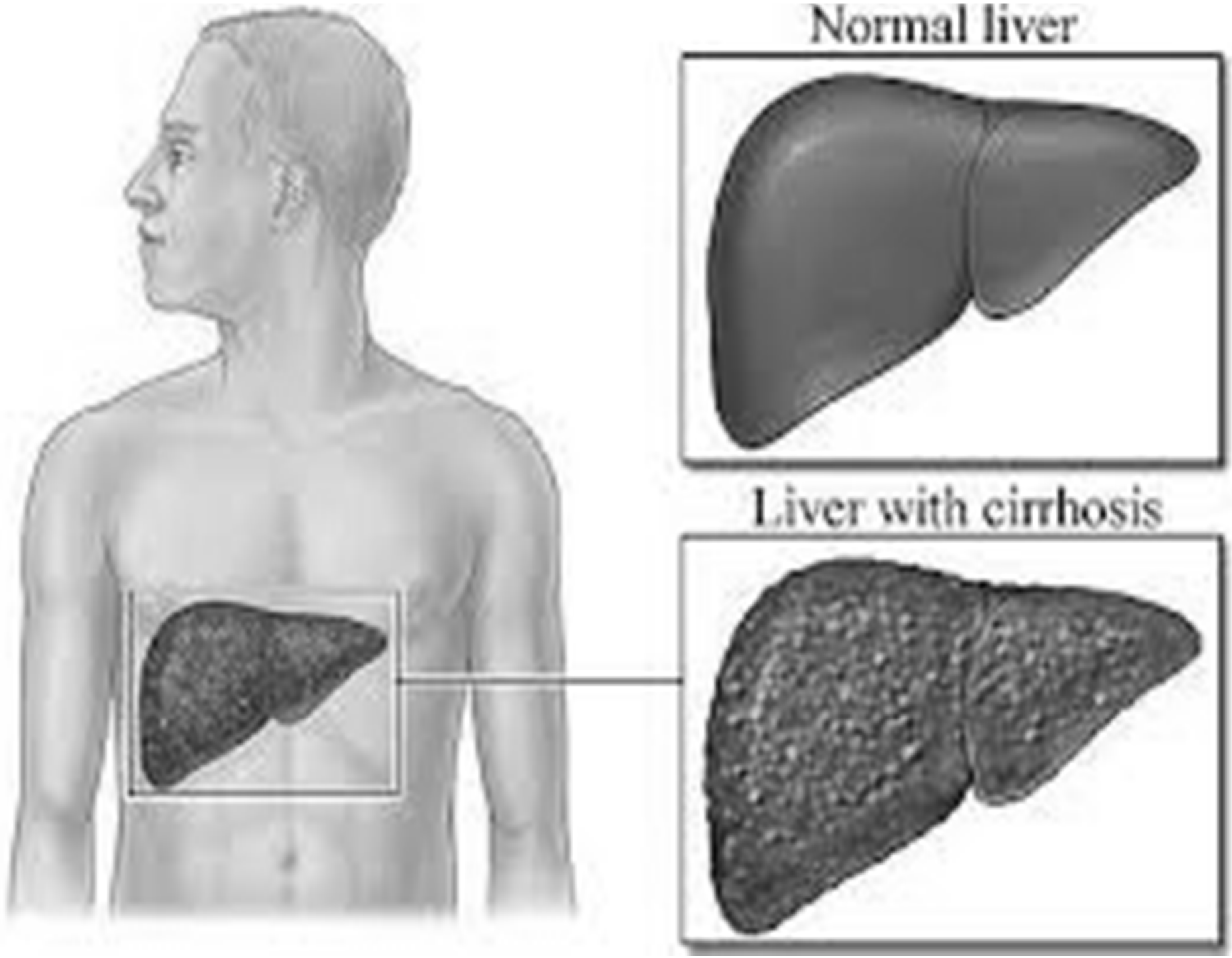
*ILO'S

*Definitions.
*Etiology.
*pathophisiology
*Clinical presentations
*Complications
*Prognosis
*Laboratory investigations
*treatment

*The word *cirrhosis* is derived from the Greek word *kirrhos*, meaning orange or tawny,

and *osis*, meaning condition.




Normal liver
Liver with cirrhosis

*Definition:

Cirrhosis is defined histologically as:

a diffuse process characterized by loss of hepatic parenchyma, formation of fibrous septa and structurally abnormal nodules, resulting in the distortion of the normal architecture , gross vascular anatomy and microcirculation.

*A hepatocyte is a cell of the main tissue of the liver. Hepatocytes make up 70-85% of the liver's cytoplasmic mass. These cells are involved in:

*Protein synthesis

*Protein storage

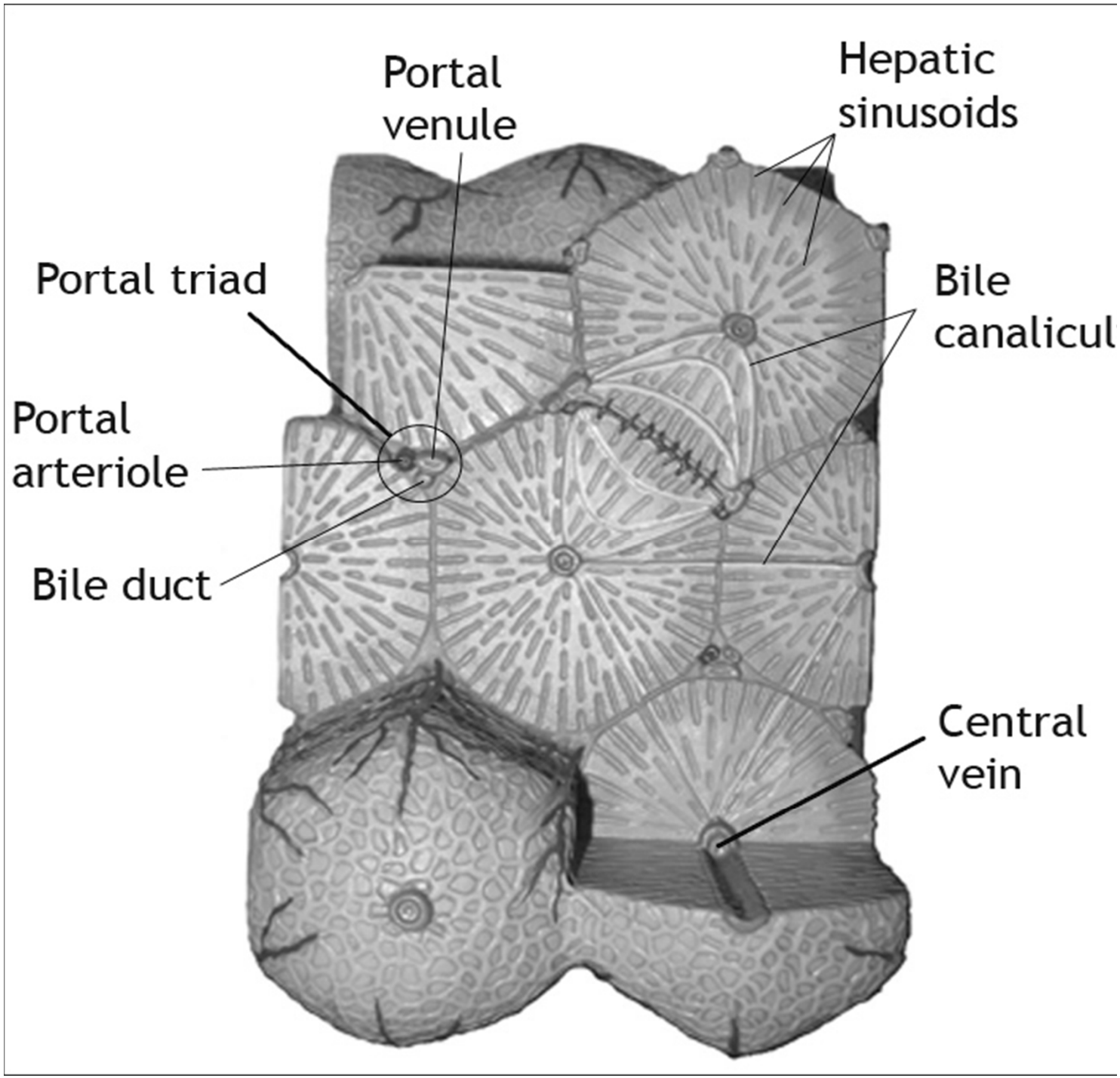
*Transformation of carbohydrates

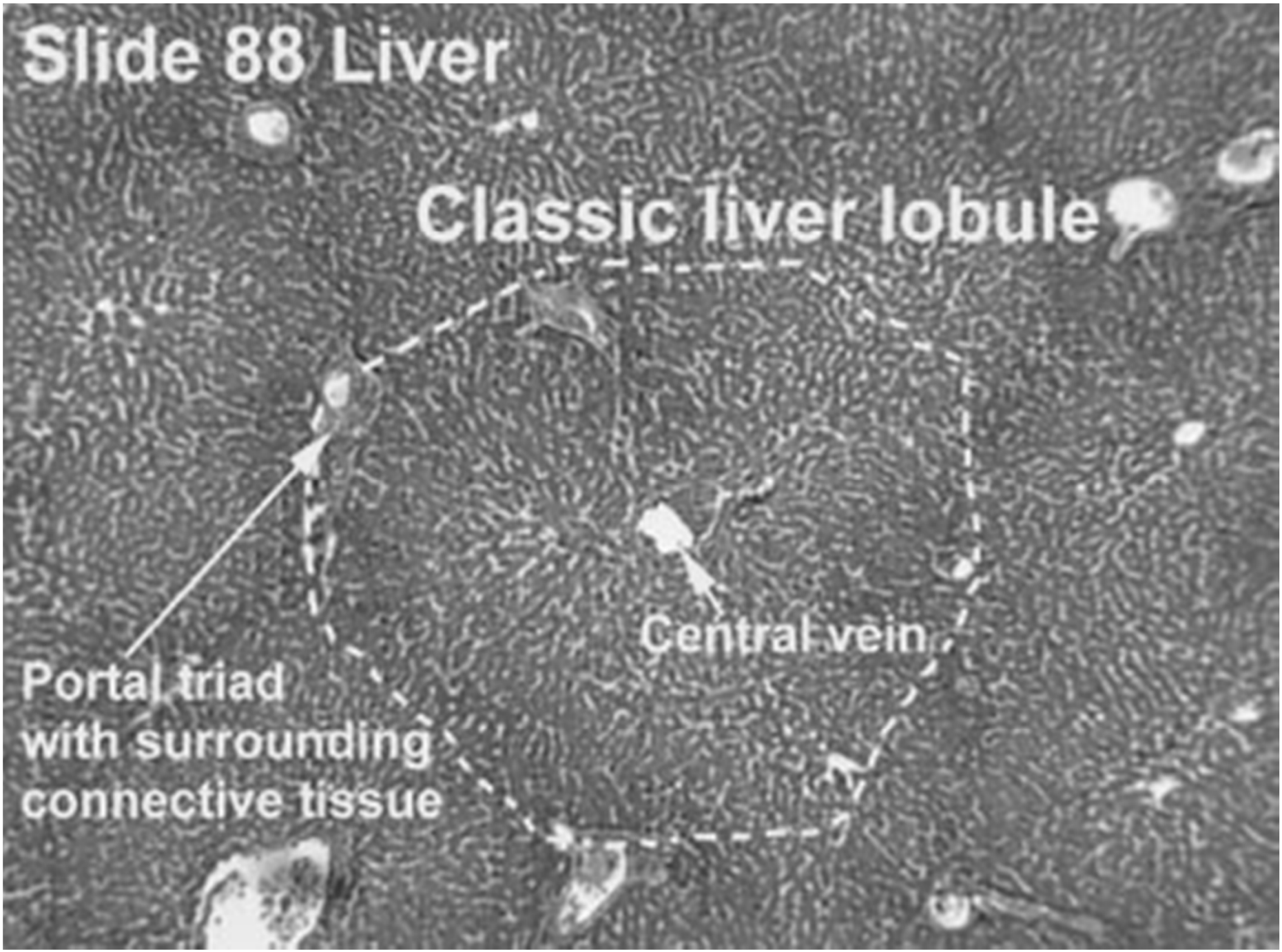
*Synthesis of cholesterol, bile salts and phospholipids

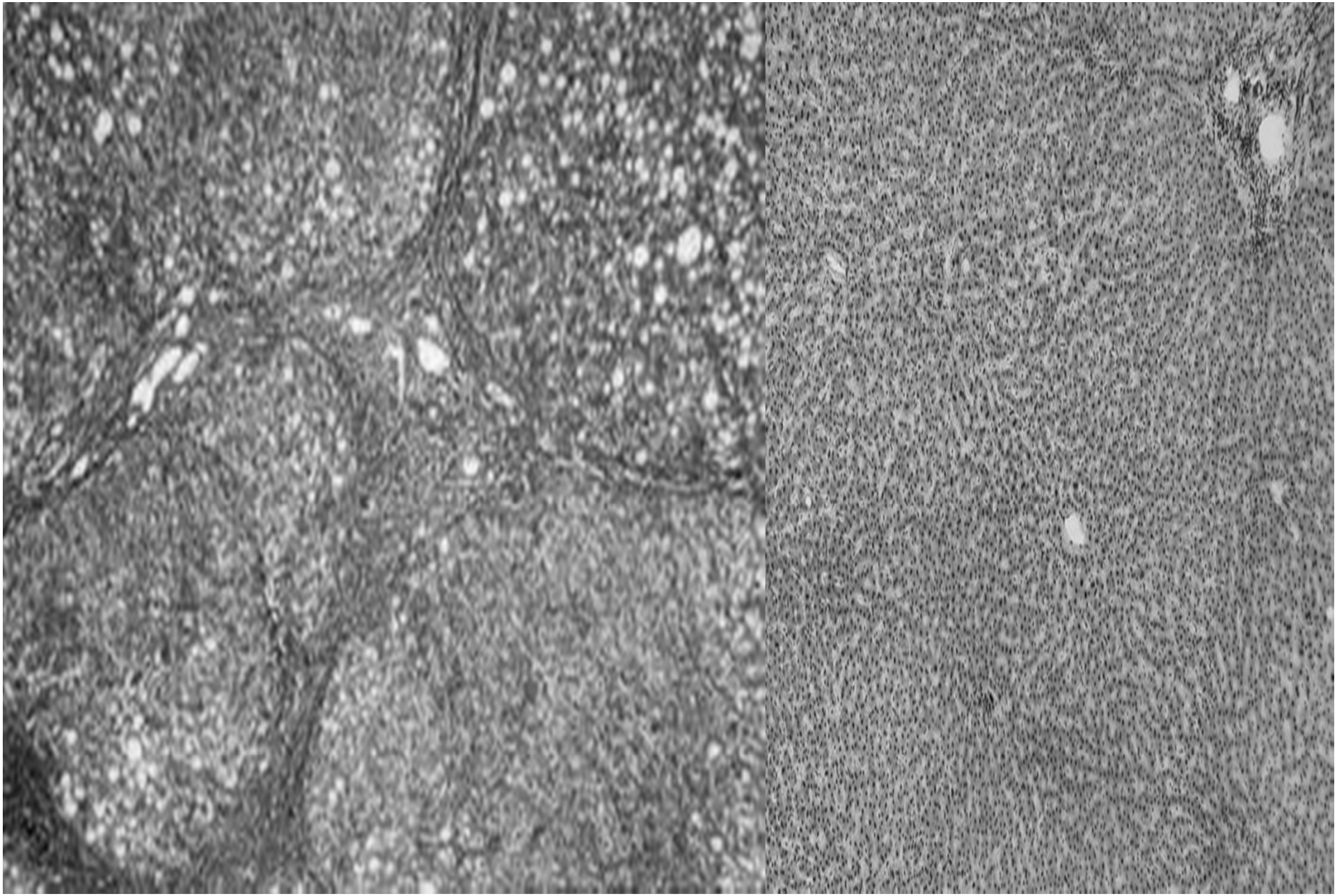
*Detoxification, modification, and excretion of exogenous and endogenous substances

*The hepatocyte also initiates formation and secretion of bile.

*Hepatic lobule



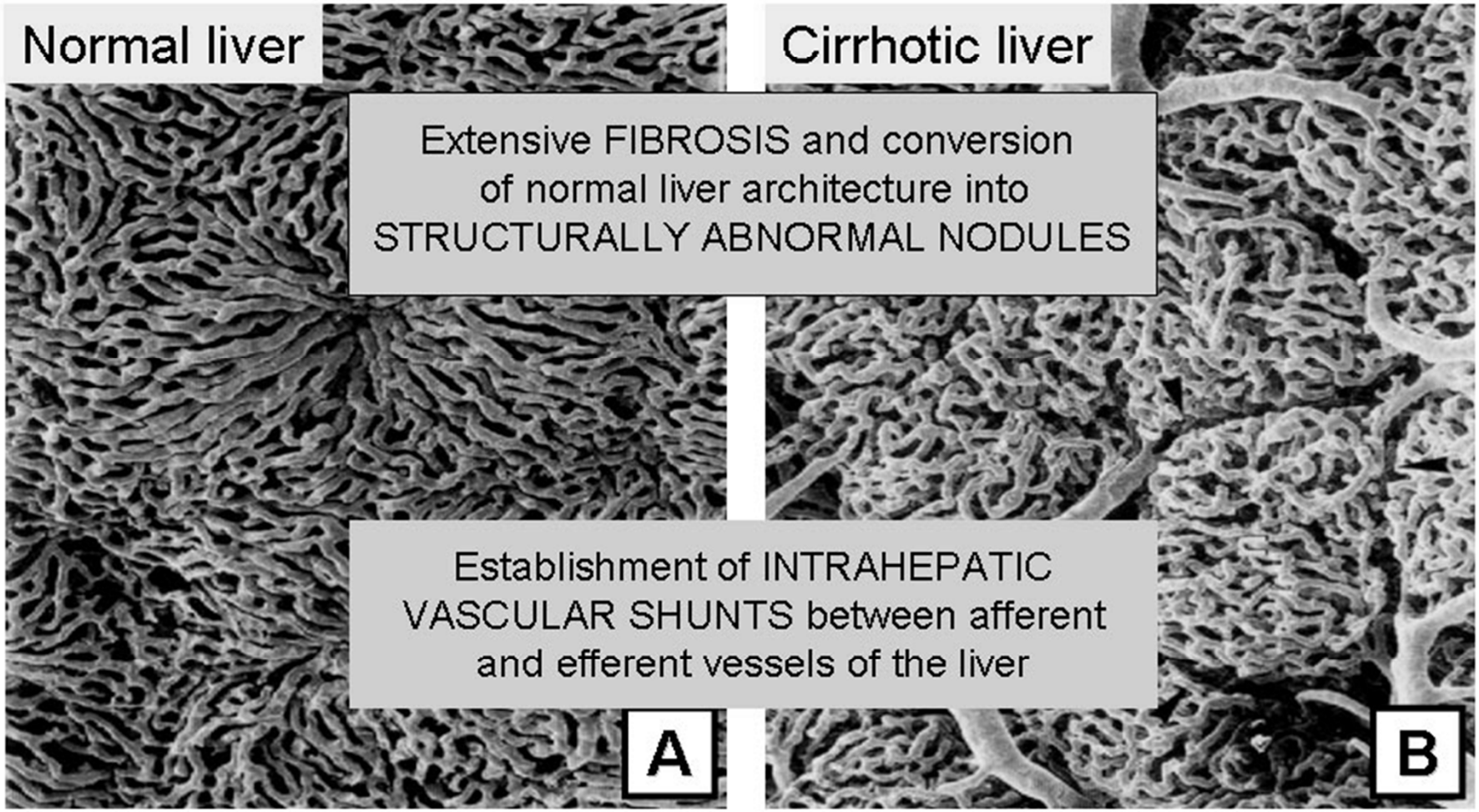

Slide 88 Liver
Classic liver lobule
Central vein
Portal triad
with surrounding
connective tissue



Cirrhotic liver

Normal liver

Deranged microvascular anatomy in cirrhosis

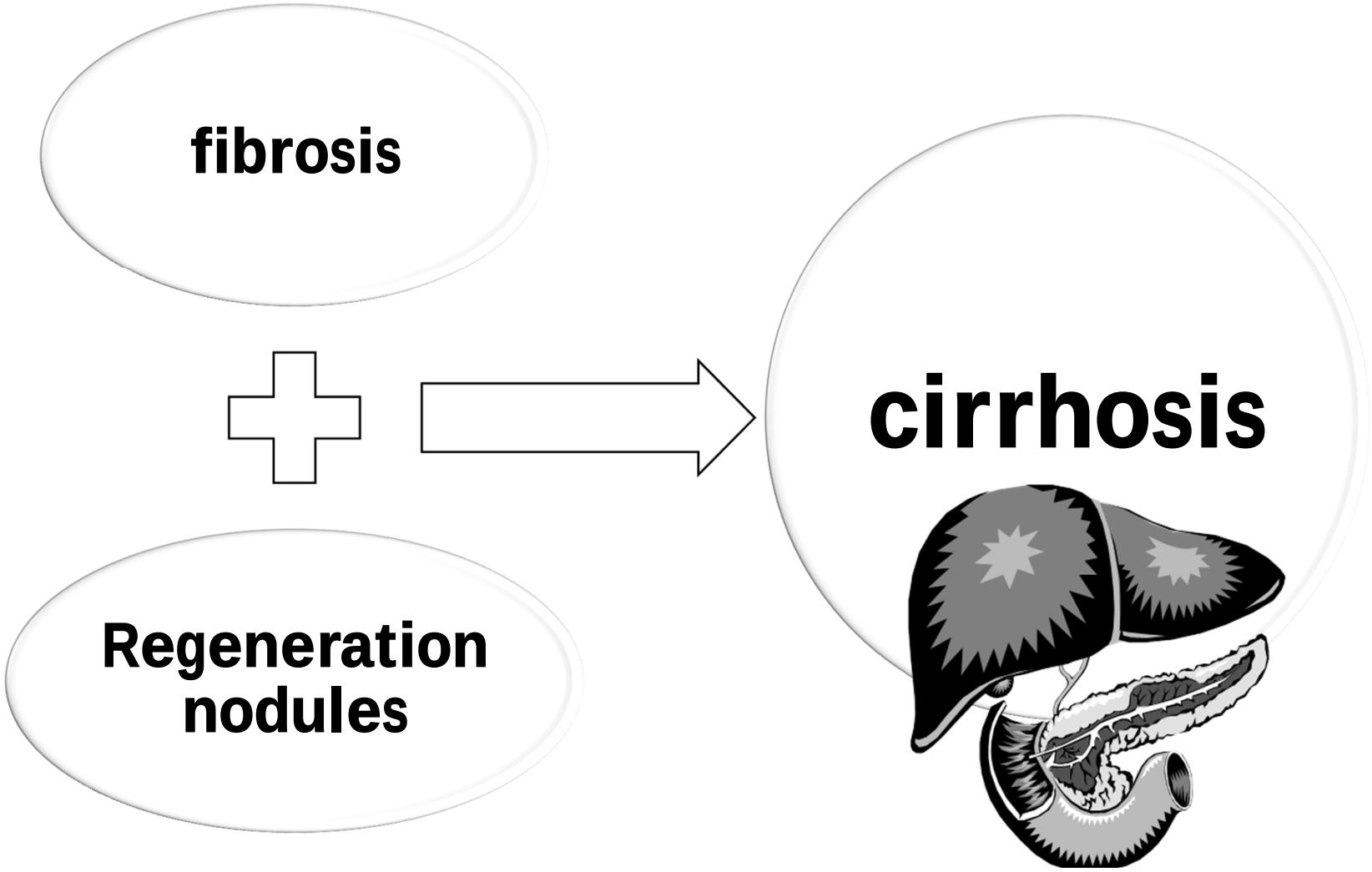


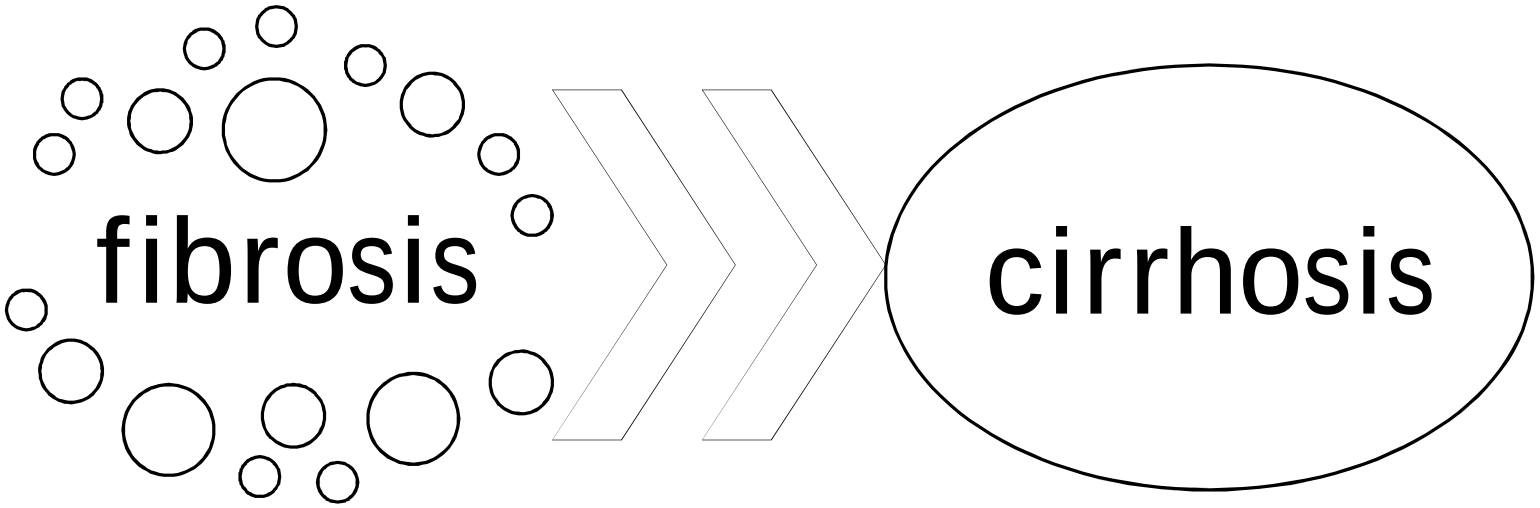
Onori et al., J Hepatol 2000; 33:555

This definition distinguishes cirrhosis from other types of liver disease that have either nodule formation or fibrosis, but not both. These hepatic disorders may be characterized by portal hypertension in the absence of cirrhosis.

Nodular regenerative hyperplasia, for example, is characterized by diffuse nodularity without fibrosis, whereas chronic **schistosomiasis** is characterized by periportal pipestem fibrosis with no nodularity.

Fibrosis # cirrhosis





As in chronic hepatitis

Progress to

End process

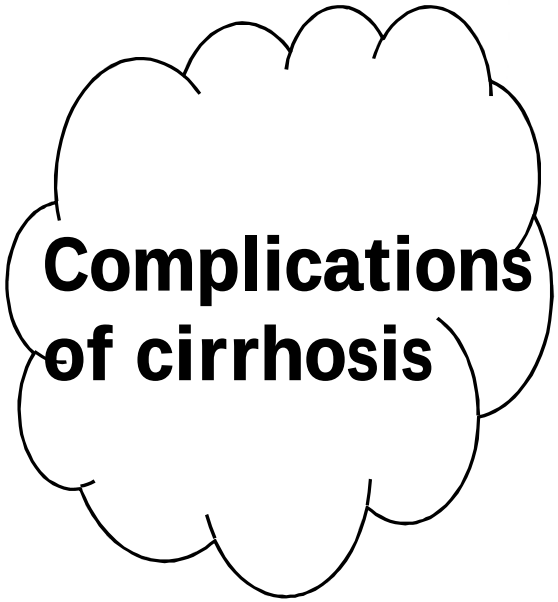
Cirrhosis represents the final common histologic pathway for a wide variety of chronic progressive liver diseases .

The progression of liver injury to cirrhosis may occur over weeks to years.

Indeed, patients with hepatitis C may have chronic hepatitis for as long as 40 years before progressing to cirrhosis.

Structural changes in the liver may cause impairment of hepatic function manifested as

* jaundice
* portal hypertension and varices
* ascites
* hepatorenal syndrome
* spontaneous bacterial peritonitis
* hepatic encephalopathy
* progressive hepatic failure



*Classification of cirrhosis :

Morphological classification

*Micronodular cirrhosis.

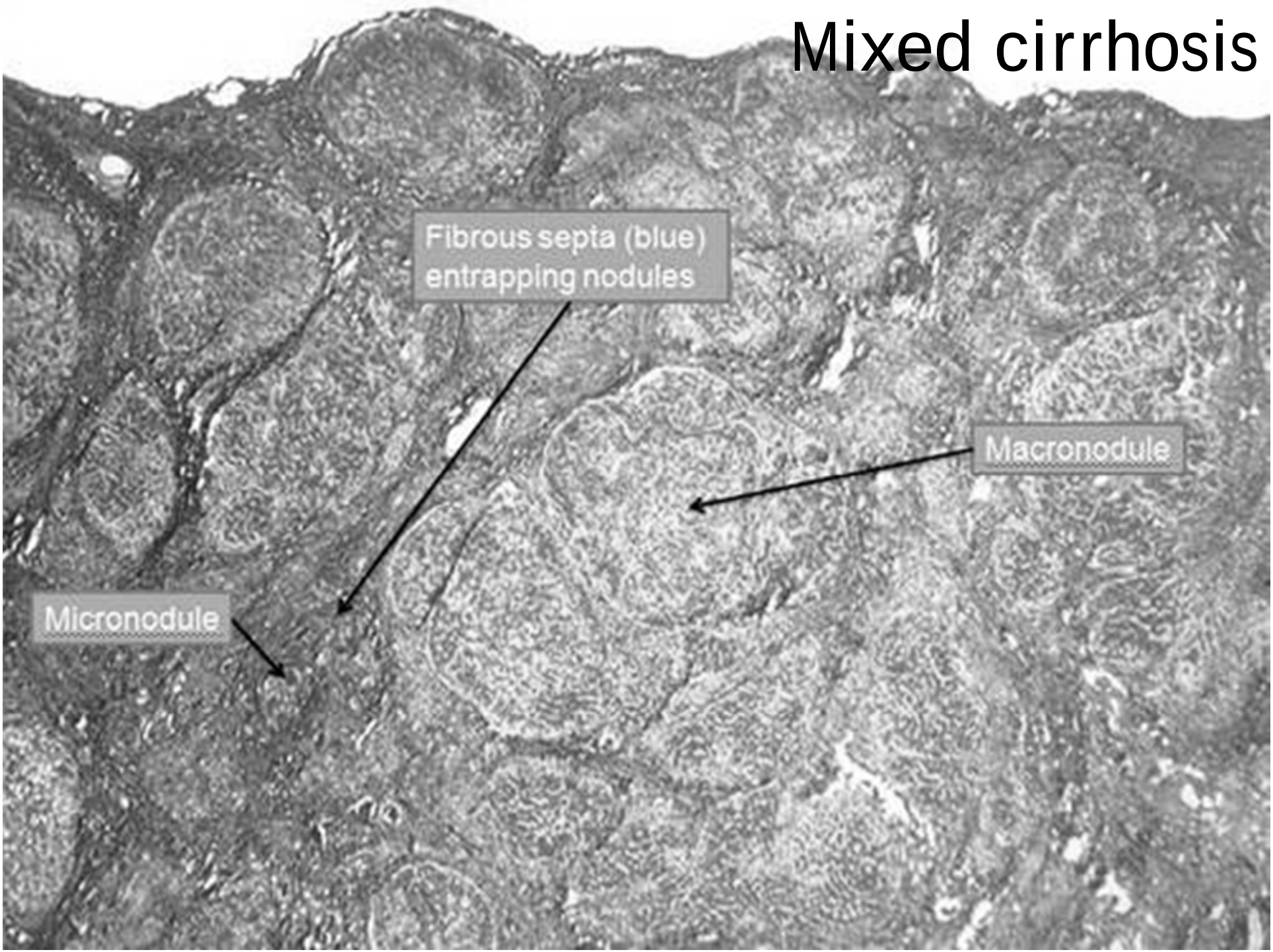
Characterized by thick , regular septa, by regenerating small nodules varying little in size,and by involvement of every nodule.

*Macronodular cirrhosis.

Characterized by septa and nodules of variable sizes and by normal lobules in larger nodules.

*Mixed cirrhosis.

Mixed cirrhosis



* **Micronodular cirrhosis**, with uniform nodules less than 3 mm in diameter: causes include alcohol, hemochromatosis, biliary obstruction, hepatic venous outflow obstruction, jejunoileal bypass, and Indian childhood cirrhosis.
* **Macronodular cirrhosis**, with nodular variation greater than 3 mm in diameter: causes include chronic hepatitic C, chronic hepatitis B, alpha-1 antitrypsin deficiency, and primary biliary cirrhosis,
* **Mixed cirrhosis**, a combination of micronodular and macronodular cirrhosis

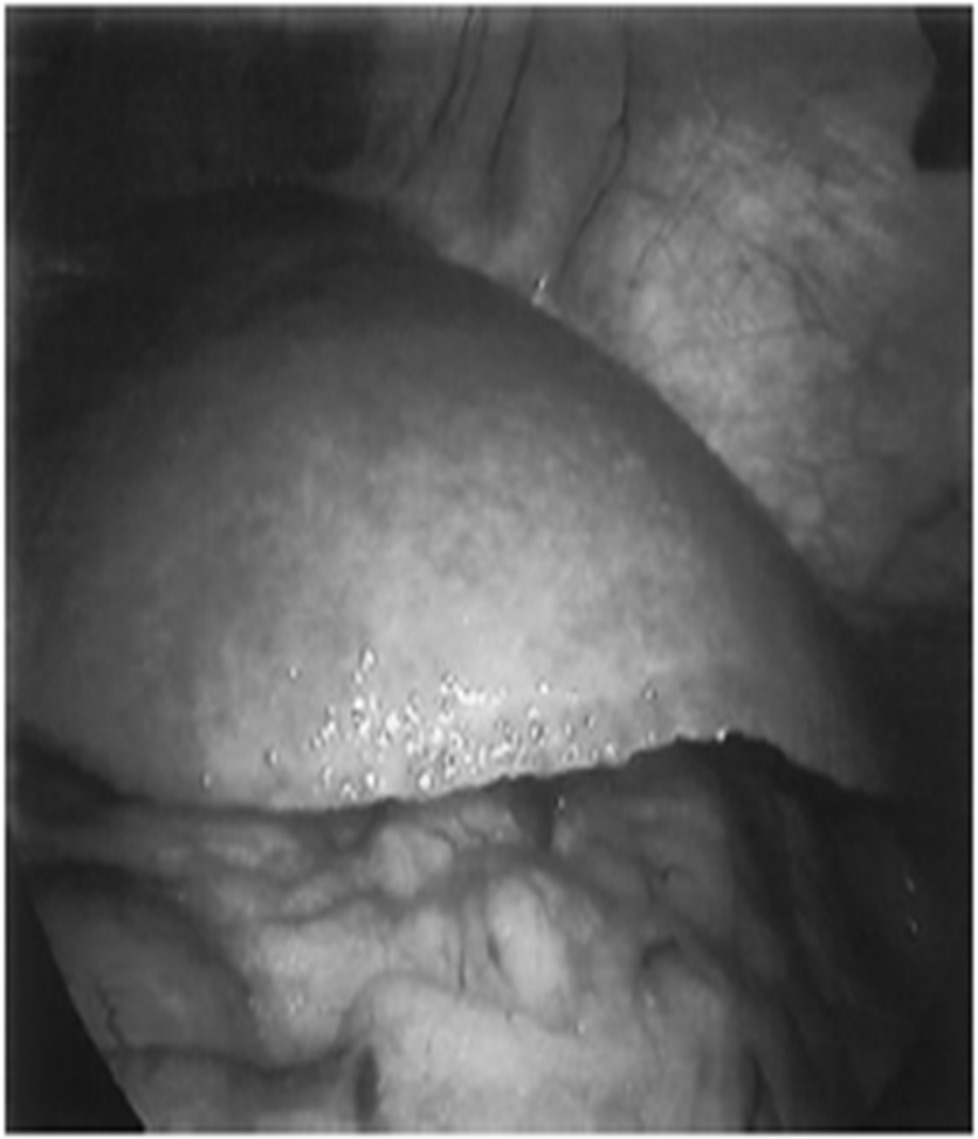


Fig. 79.1 Laparoscopic appearance of micronodular alcoholic liver cirrhosis. At first glance the liver surface looks smooth.

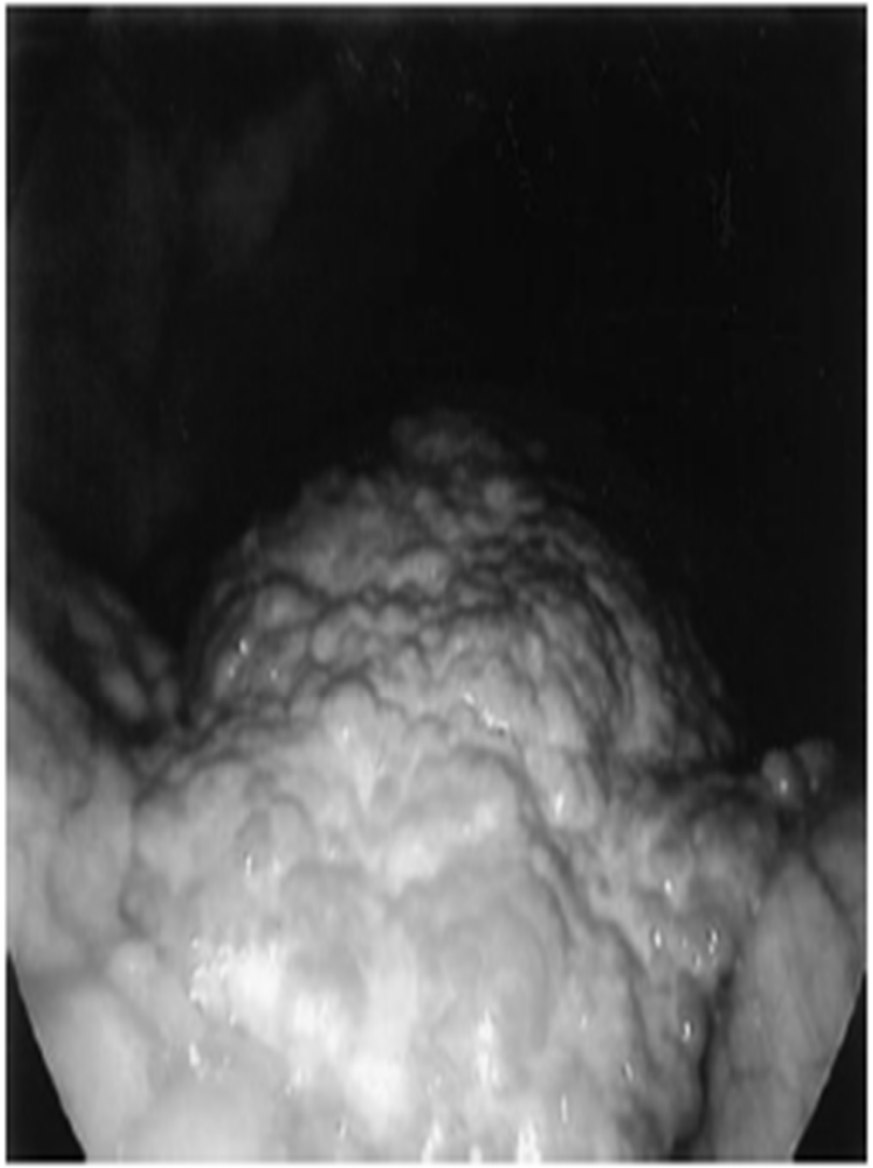


Fig. 79.3 Macronodular liver cirrhosis

Regeneration in a micronodular cirrhosis results in a macronodular or mixed appearance. With time, micronodular cirrhosis often converts to macronodular cirrhosis.

So,

Morphologic classification is less useful because of considerable overlap.

*Etiological classification

An etiologic classification of cirrhosis is more clinically relevant than a morphologic one, because the cause can be determined in most cases, and important management issues such as family counseling, vaccination, and specific therapy are best addressed once the cause has been determined.

Etiology	Diagnostic evaluation
Infection	
Hepatitis B	HBsAg, anti-HBs, anti-HBc, HBV DNA
Hepatitis C	Anti-HCV, HCV RNA
Hepatitis D	Anti-HDV
Toxins	
Alcohol	History, AST/ALT ratio, liver biopsy
Cholestasis	
Primary biliary cirrhosis	AMA, IgM, liver biopsy
Secondary biliary cirrhosis	MRCP, ERCP, liver biopsy
Primary sclerosing cholangitis	MRCP, ERCP, liver biopsy
Autoimmune	
Autoimmune hepatitis	ANA, IgG level smooth muscle antibodies, liver-kidney microsomal antibodies, liver biopsy

*Etiology of cirrhosis :

Vascular	
Cardiac cirrhosis	Echocardiogram, liver biopsy
Budd–Chiari syndrome	CT, US, MRI/MRA,
Sinusoidal obstruction syndrome	History of offending drug use, liver biopsy
Metabolic	
Hemochromatosis	Iron studies, *HFE* gene mutation, liver biopsy
Wilson disease	Serum and urinary copper, ceruloplasmin, slit lamp eye examination, liver biopsy
Alpha-1 antitrypsin deficiency	Alpha-1 antitrypsin level, protease inhibitor type, liver biopsy
NASH	Liver biopsy
Cryptogenic	Exclude NASH, drugs

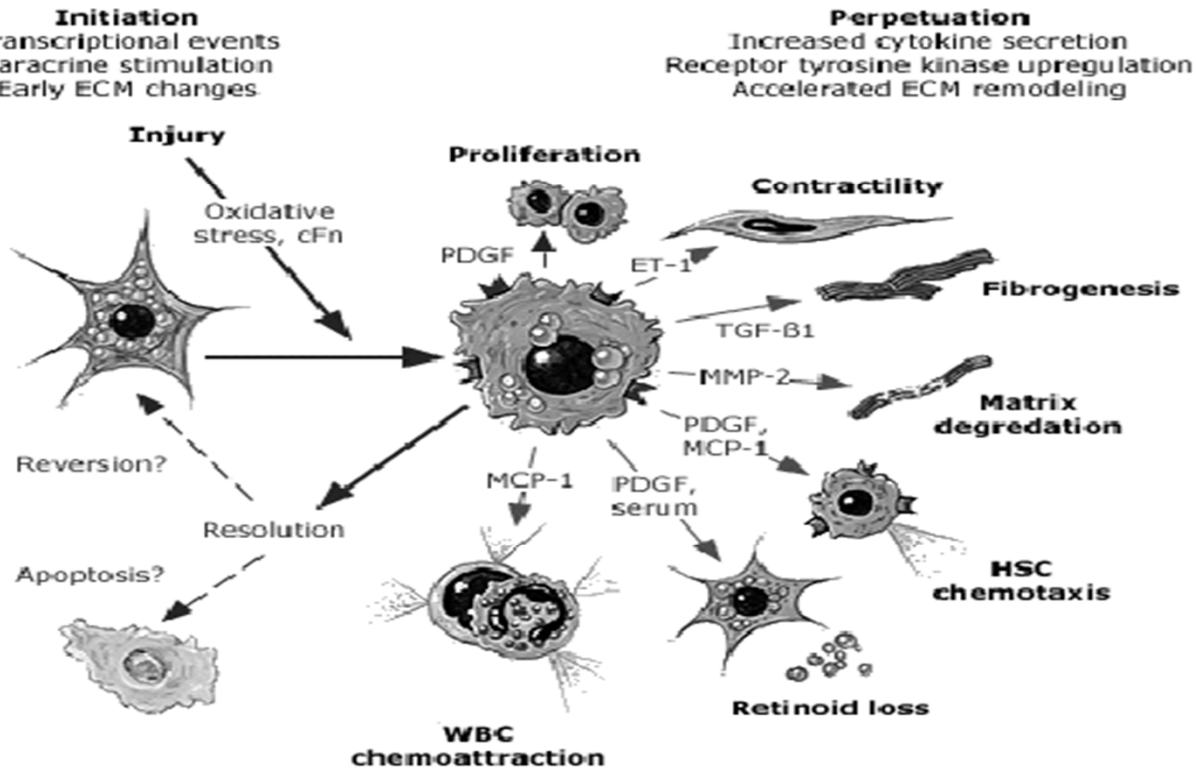
ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; anti-HDV, antibody to hepatitis D virus; AST, aspartate aminotransferase; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; HBsAg, hepatitis B surface antigen; IgG, immunoglobulin G; IgM, immunoglobulin M; MRA, magnetic resonance angiography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NASH, nonalcoholic steatohepatitis; US, ultrasonography.

PATHOPHYSIOLOGY OF HEPATIC FIBROSIS

- The development of hepatic fibrosis reflects an alteration in the normally balanced processes of extracellular matrix production and degradation. Extracellular matrix, the normal scaffolding for hepatocytes, is composed of collagens (especially types I, III, and V), glycoproteins, and proteoglycans .

- Stellate cells, located in the perisinusoidal space, are essential for the production of extracellular matrix. Stellate cells, which were once known as **Ito cells, lipocytes, or perisinusoidal cells**, may become activated into collagen-forming cells by a variety of paracrine factors. Such factors may be released by hepatocytes, Kupffer cells, and sinusoidal endothelium following liver injury. As an example, increased levels of the cytokine transforming growth factor beta1 (TGF-beta1) are observed in patients with chronic hepatitis C and those with cirrhosis. TGF-beta1, in turn, stimulates activated stellate cells to produce type I collagen.

Phenotypic features of hepatic stellate cell activation during liver injury and resolution

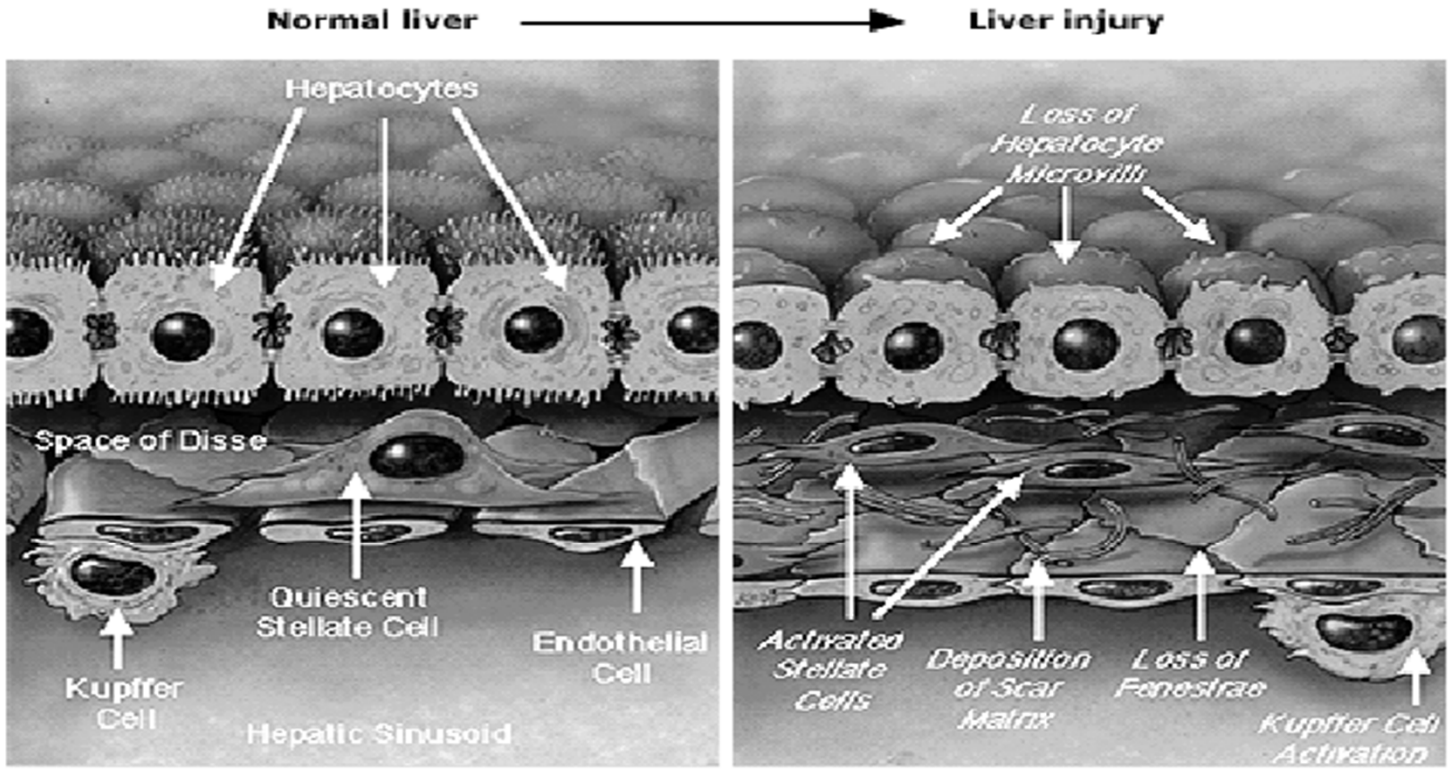


Following liver injury, hepatic stellate cells undergo "activation," which connotes a transition from quiescent vitamin A-rich cells into proliferative, fibrogenic and contractile myofibroblasts. The major phenotypic changes after activation include proliferation, contractility, fibrogenesis, matrix degradation, chemotaxis, retinoid loss, and white blood cell chemoattraction. Key mediators underlying these effects are shown. The fate of activated stellate cells during resolution of liver injury is uncertain but may include reversion to a quiescent phenotype and/or selective clearance by apoptosis.

Courtesy of Scott L Friedman, MD.

- Increased collagen deposition in the space of Disse (the space between hepatocytes and sinusoids) and the diminution of the size of endothelial fenestrae lead to the capillarization of sinusoids. Activated stellate cells also have contractile properties. Both capillarization and constriction of sinusoids by stellate cells contribute to the development of portal hypertension.

Sinusoidal events during fibrosing liver injury



Changes in the subendothelial space of Disse and sinusoid as fibrosis develops in response to liver injury include alterations in both cellular responses and extracellular matrix composition. Stellate cell activation leads to accumulation of scar (fibril-forming) matrix. This in turn contributes to the loss of hepatocyte microvilli and sinusoidal endothelial fenestrae, which result in deterioration of hepatic function. Kupffer cell (macrophage) activation accompanies liver injury and contributes to paracrine activation of stellate cells.

Courtesy of Scott L Friedman, MD.

Increased intrahepatic resistance in cirrhosis

Architectural disturbances

Distortion of vascular architecture by fibrosis, scarring, regenerative nodules.
Thrombosis

Mechanical Component
("fixed")

~70 %

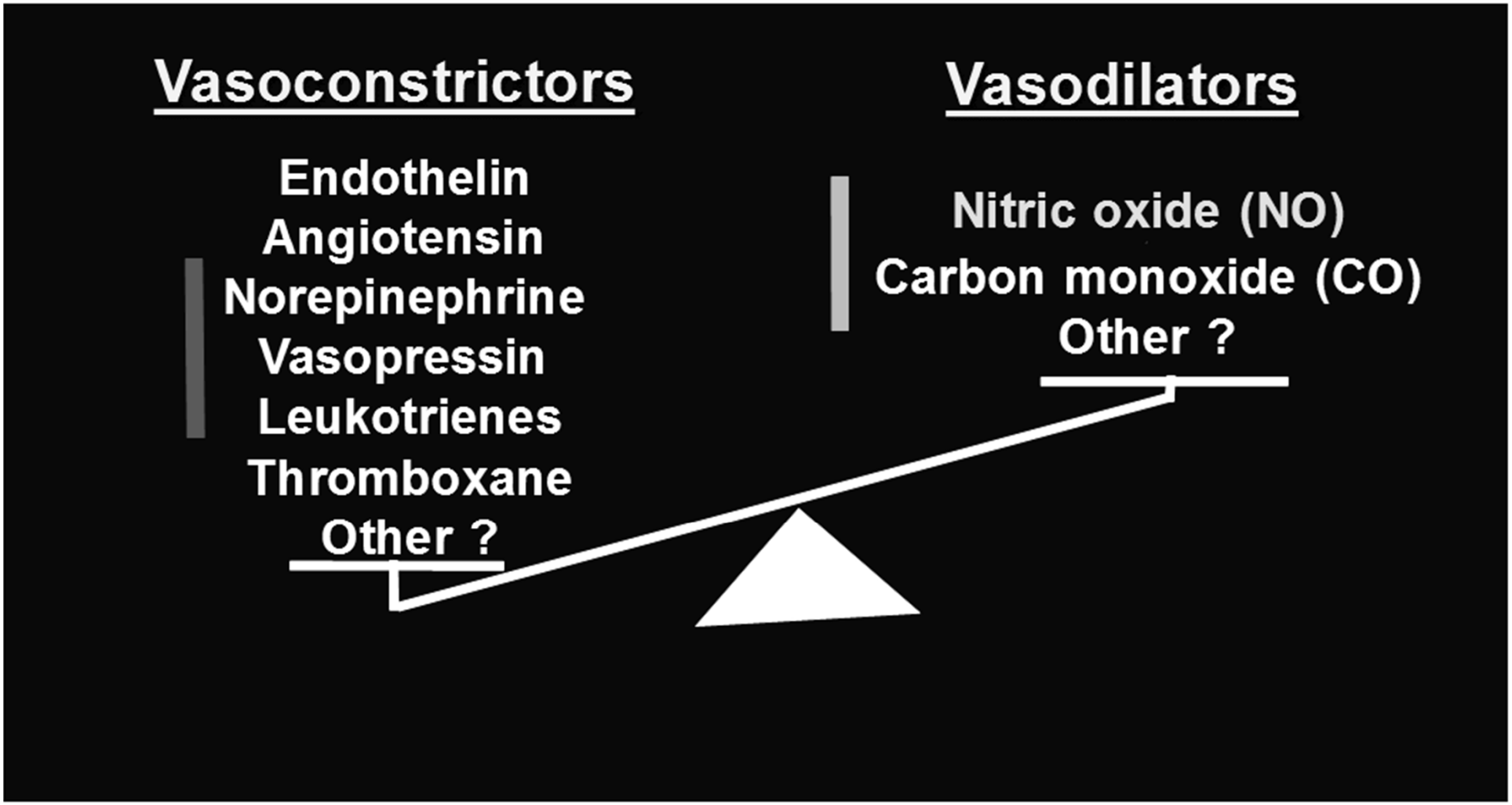
Functional alterations

Active contraction of hepatic stellate cells, vascular smooth cells in the portal venules, and myofibroblasts

Dynamic Component
(modifiable by drugs)

~30 %

Vasodilator/vasoconstrictor imbalance in the pathogenesis of increased intrahepatic vascular resistance in cirrhosis



*Clinical features :

Cirrhosis results in two major clinical events :

1-Manifestations of hepato-cellular failure.

2-Manifestations of portal hypertention.

*Clinical presentations :

The manifestations of cirrhosis are protean. Patients with cirrhosis may come to clinical attention in numerous ways

*Clinical presentations :

1. Stigmata of chronic liver disease on physical examination
2. Abnormal serum chemistry test results and hematologic indices (e.g., serum aminotransferases, bilirubin, alkaline phosphatase, albumin, prothrombin time, and platelet count)
3. Radiographic abnormalities (e.g., small, shrunken, nodular liver on ultrasound or computed tomographic [CT] examination)

*Clinical presentations :

4. Complications of decompensated liver disease (e.g., ascites, variceal hemorrhage)
5. Cirrhotic appearance of the liver at the time of laparotomy or laparoscopy

*Features of hepatocellular failure

*Compensated cirrhosis :

*The disease may be discovered at a routine examination or biochemical screen.

*Cirrhosis may be suspected if the patient has fatigue, mild pyrexia, vascular spiders, palmar erythema, or unexplained epistaxis or edema of the ankles.

*Firm enlargement of the liver and splenomegaly are helpful diagnostic signs.

*Decompensated cirrhosis :

*The patient usually seeks medical advice because of ascites and/or jaundice.

*General health fails with weakness, muscle wasting and weight loss.

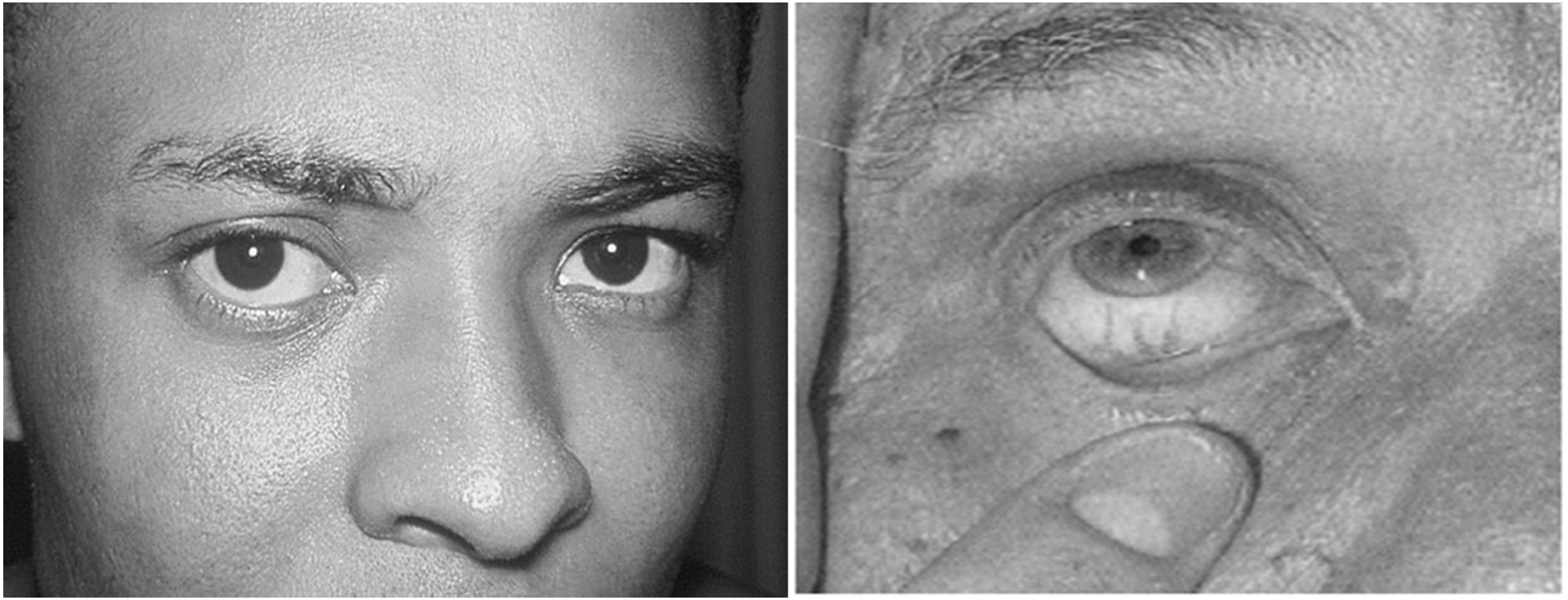
*Continuing mild fever (37.5-38c) is often due to Gram-negative bacteremia.

*Flappy tremors may be present due to hepatic encephalopathy.

*Jaundice implies that liver cell destruction exceeds the capacity for regeneration and is always serious.

SIGNS OF DECOMPENSATED HEPATOCELLULAR DISEASE

- **Jaundice**
- **Ascites**
- **Oliguric hepatic failure**
- **Hepatic encephalopathy**
- **Fetor hepaticus**
- **Asterixis**
- **Behavioral alterations (confusion, disorientation, failure to complete simple mental tasks**)



Scleral icterus

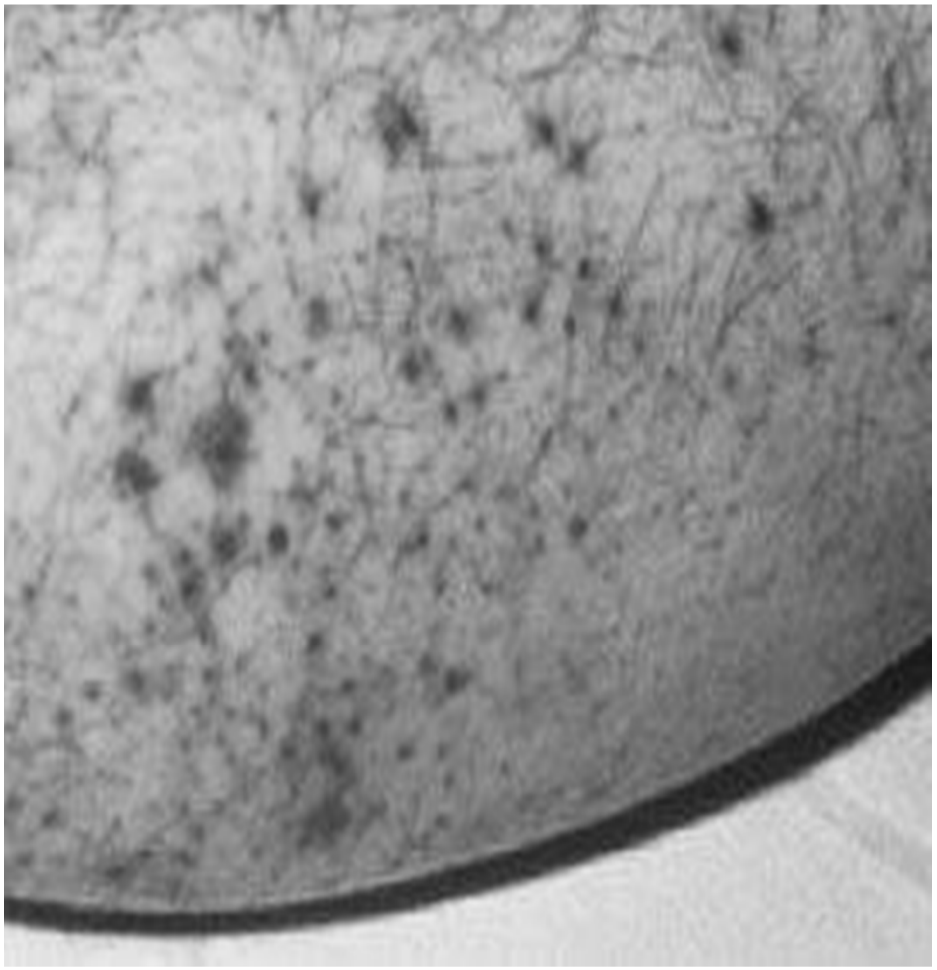
*The skin may be pigmented.

*Purpura over the arms, shoulders, and lower limbs may be associated with a low platelets count.

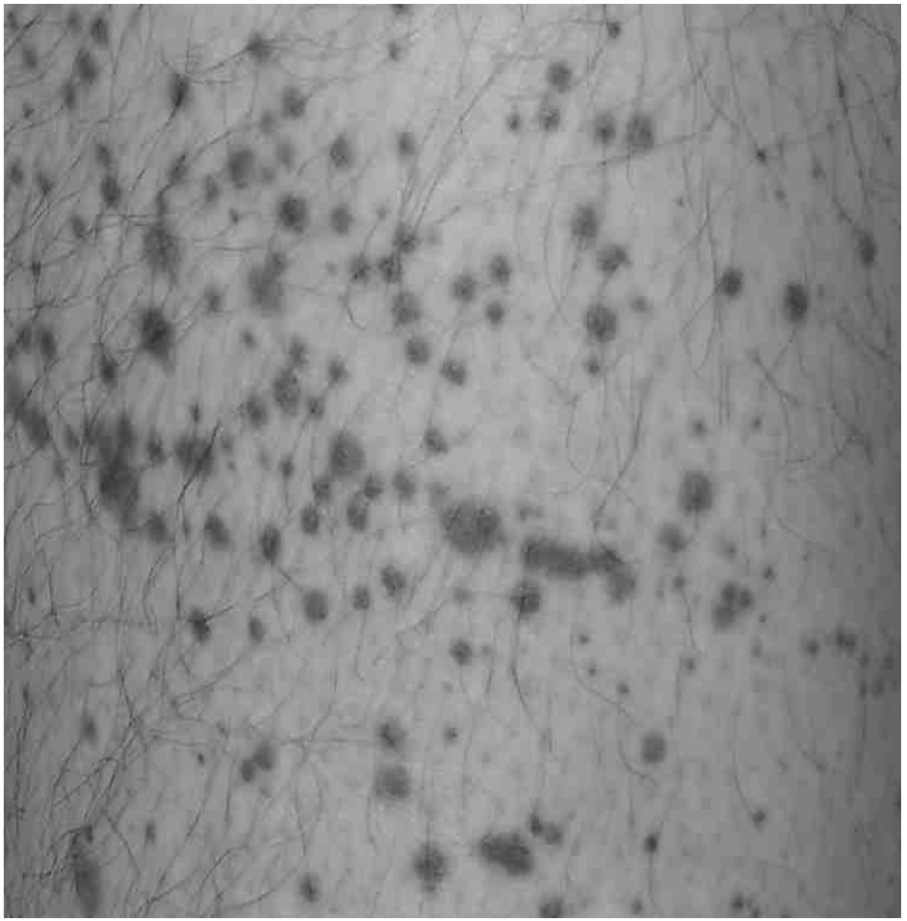
*Spontaneous bruising and epistaxis reflect a prothrombin deficiency.

*The circulation is overactive. The blood pressure is low.

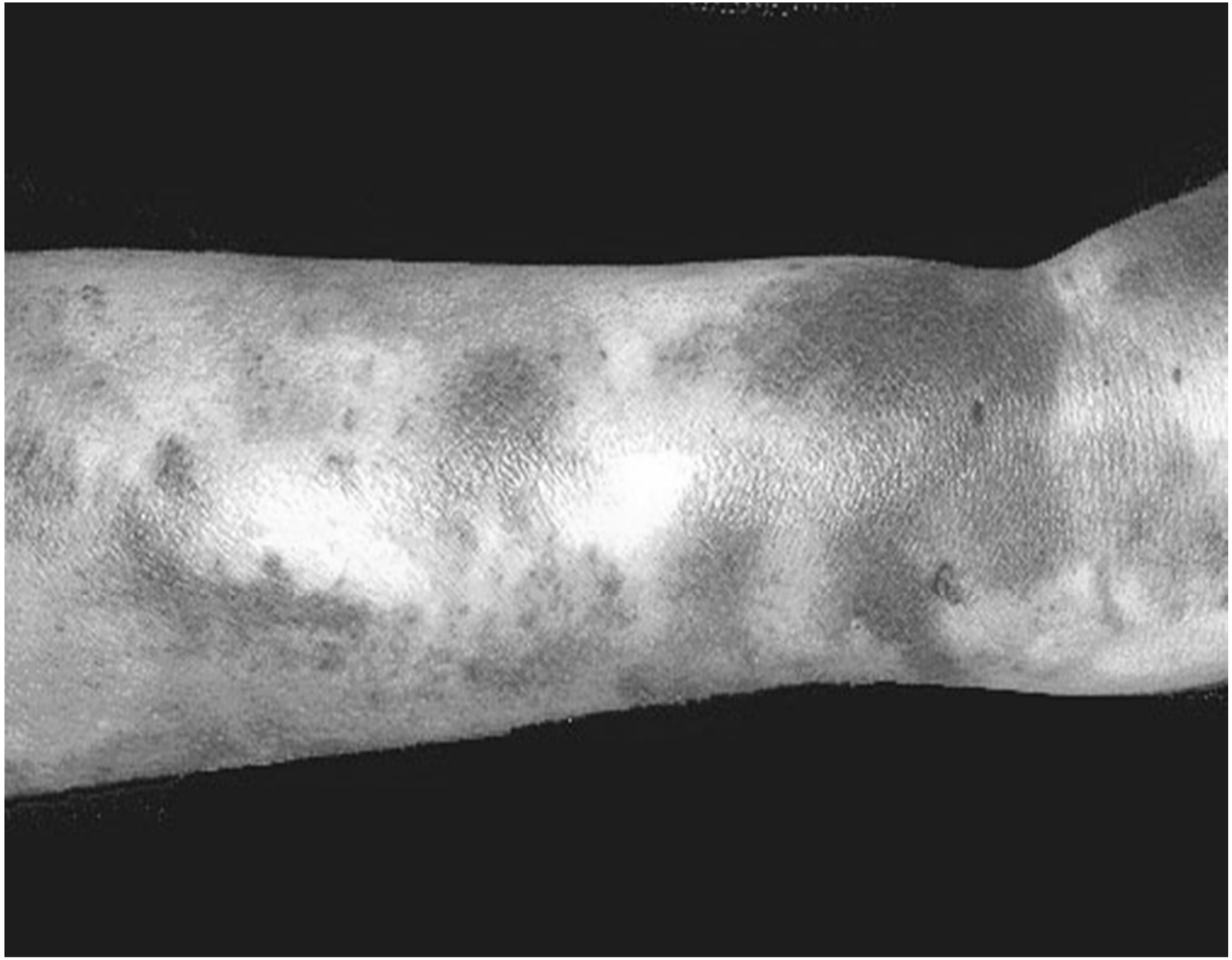
*Sparse body hair, vascular spiders, palmar erythema, white nails and gonadal atrophy and gynecomastia are common.



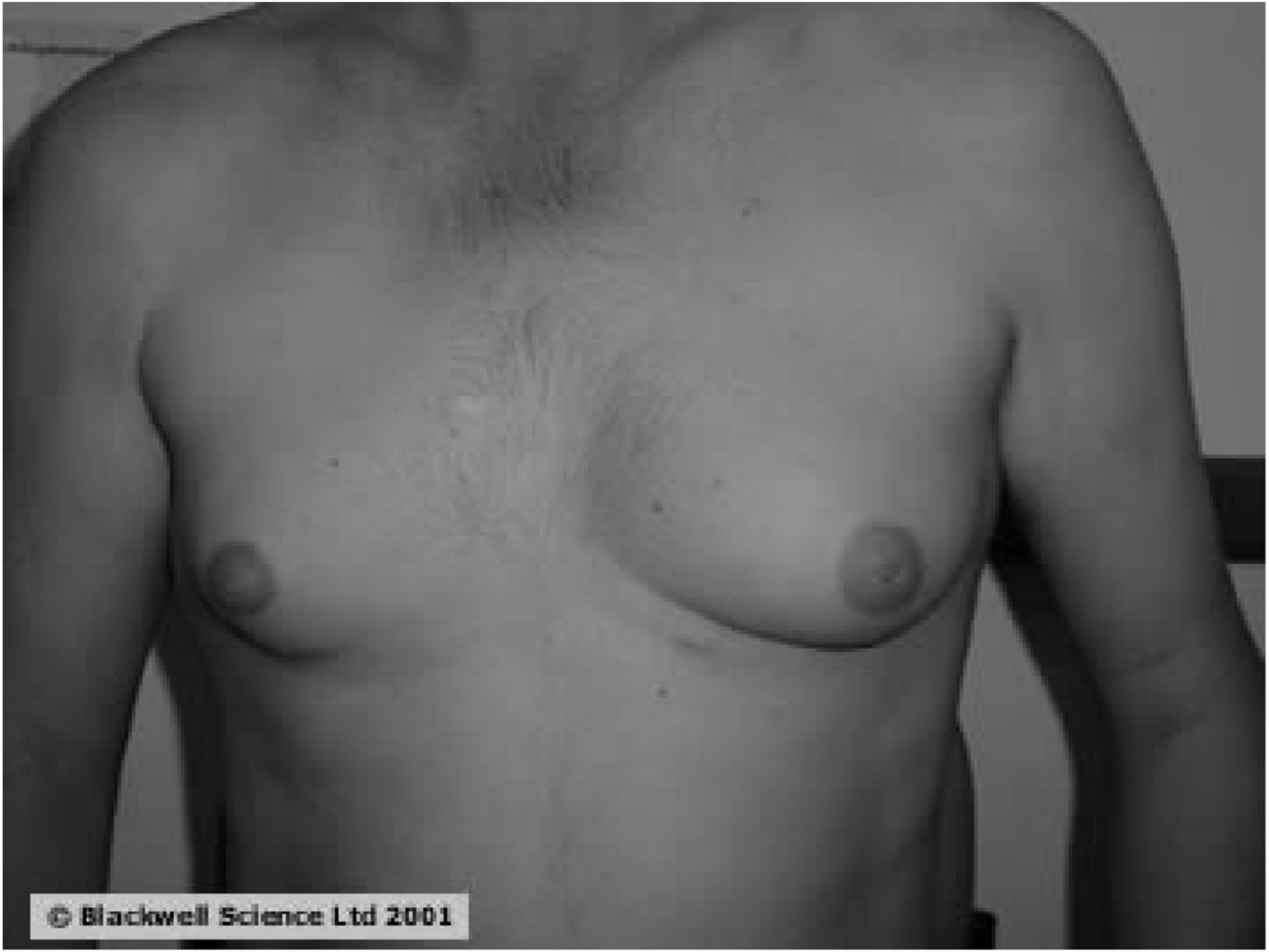
Ecchymosis and petechiae



purpura



Ecchymosis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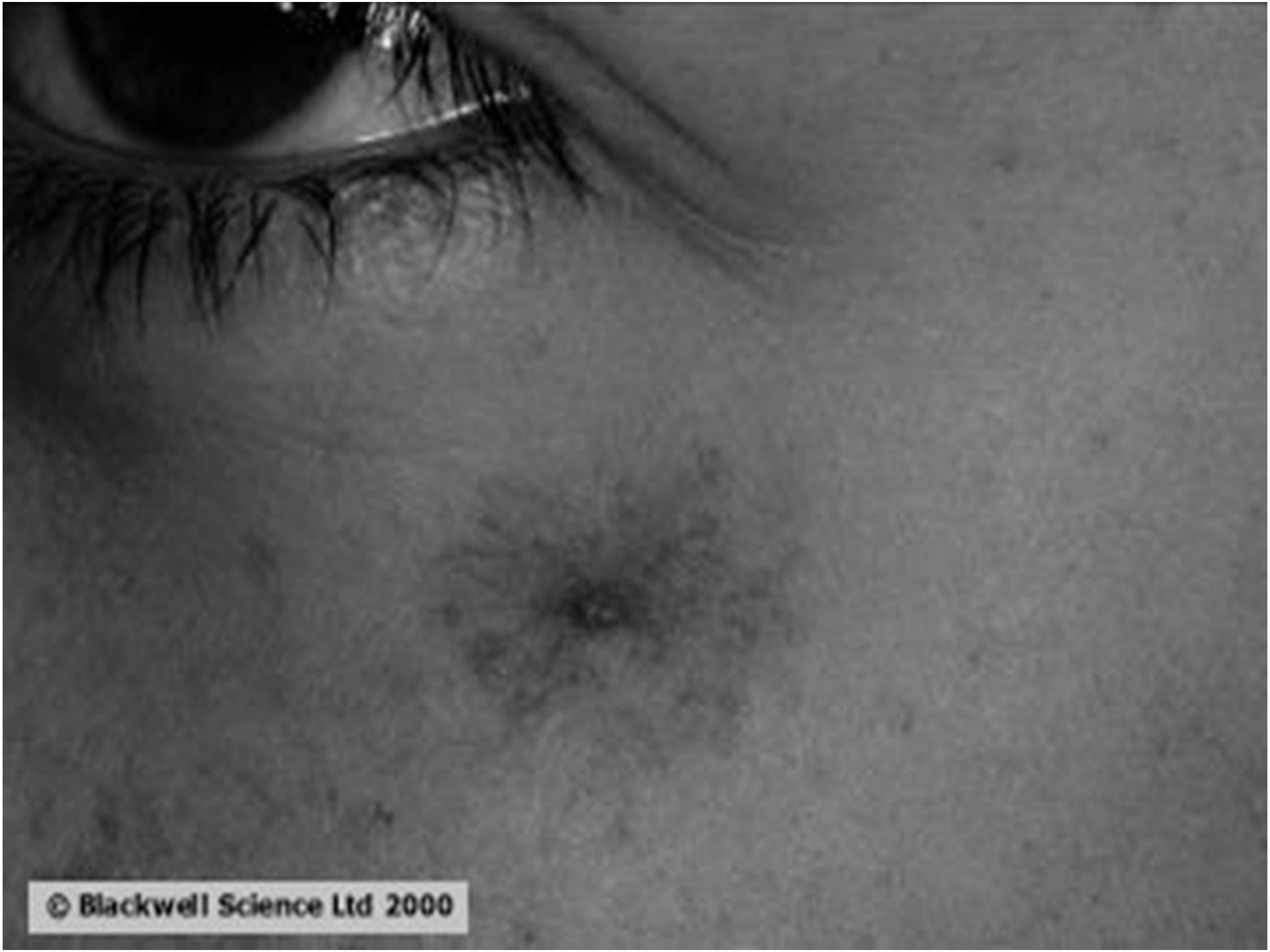
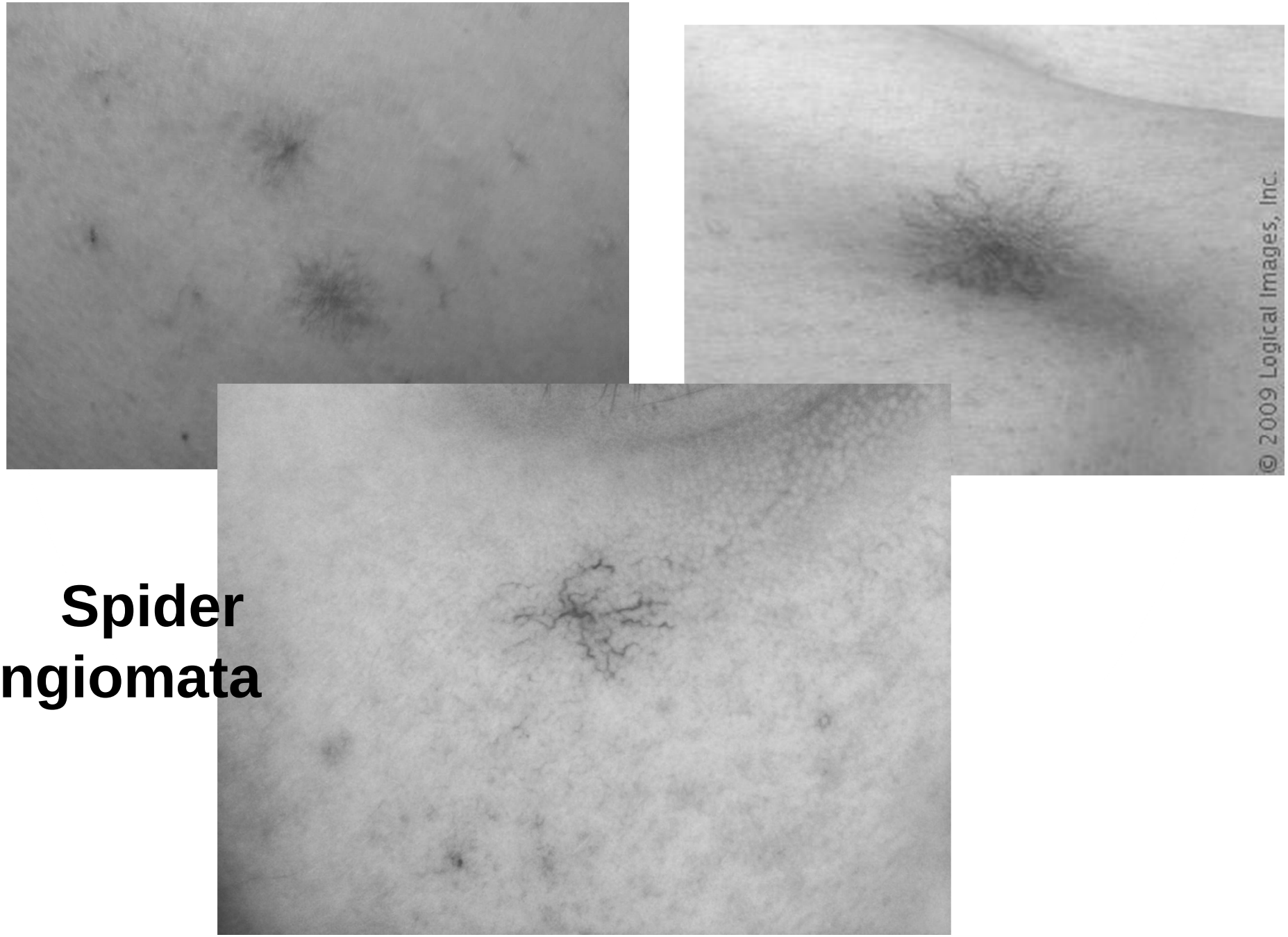
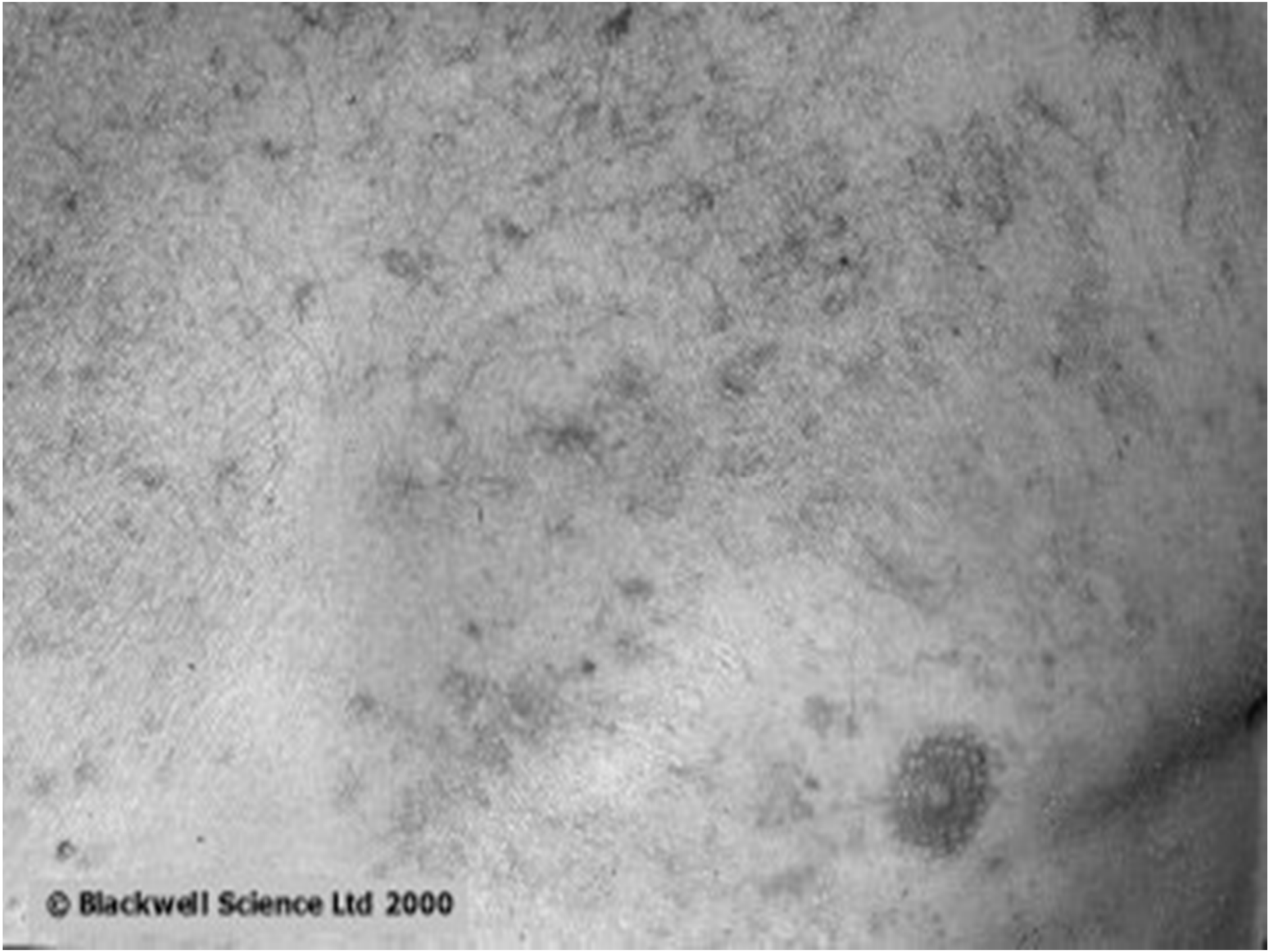
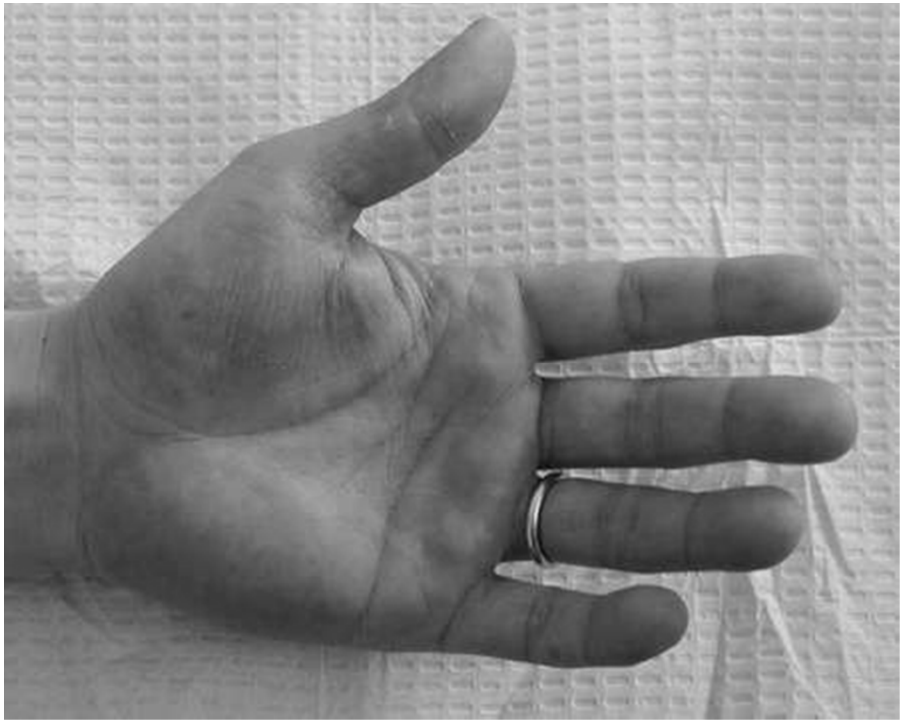


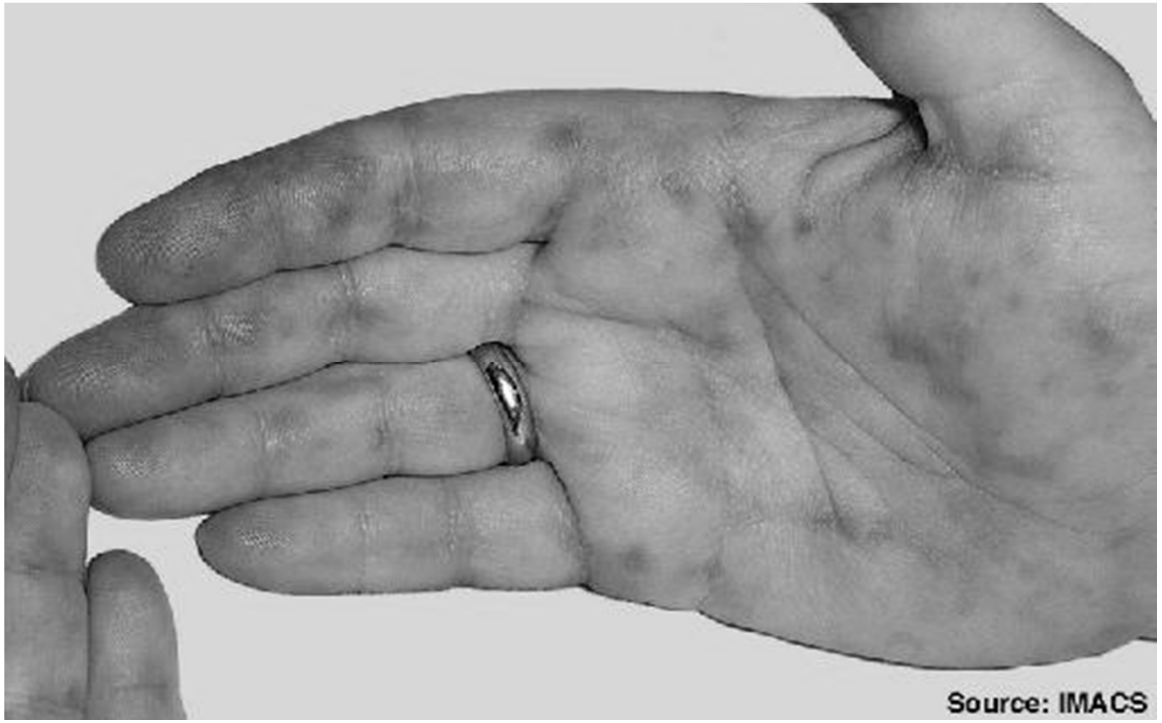


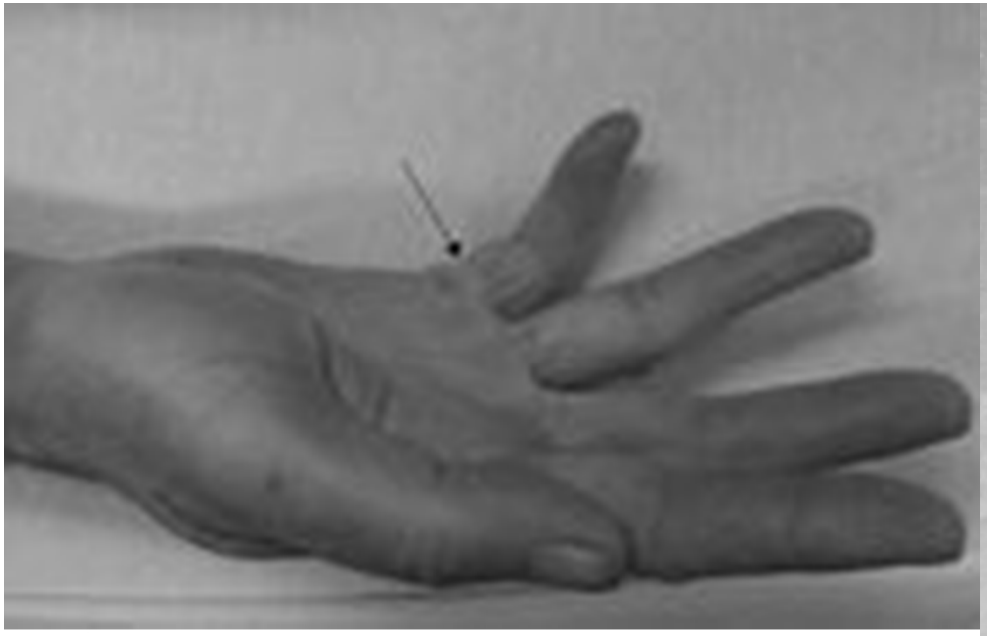
Spider angiomata

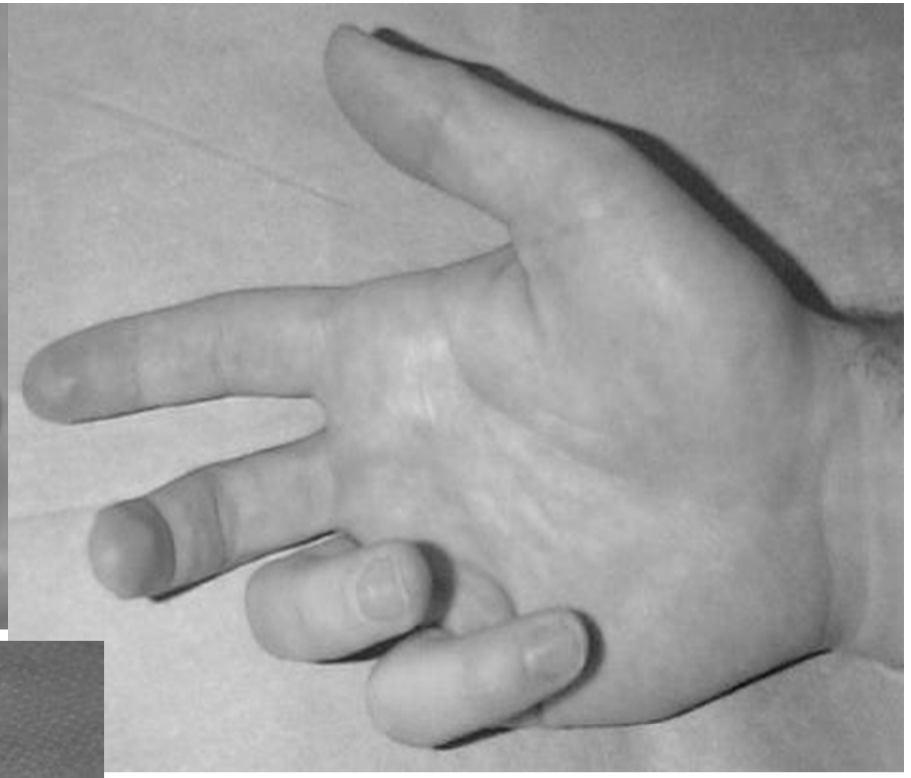


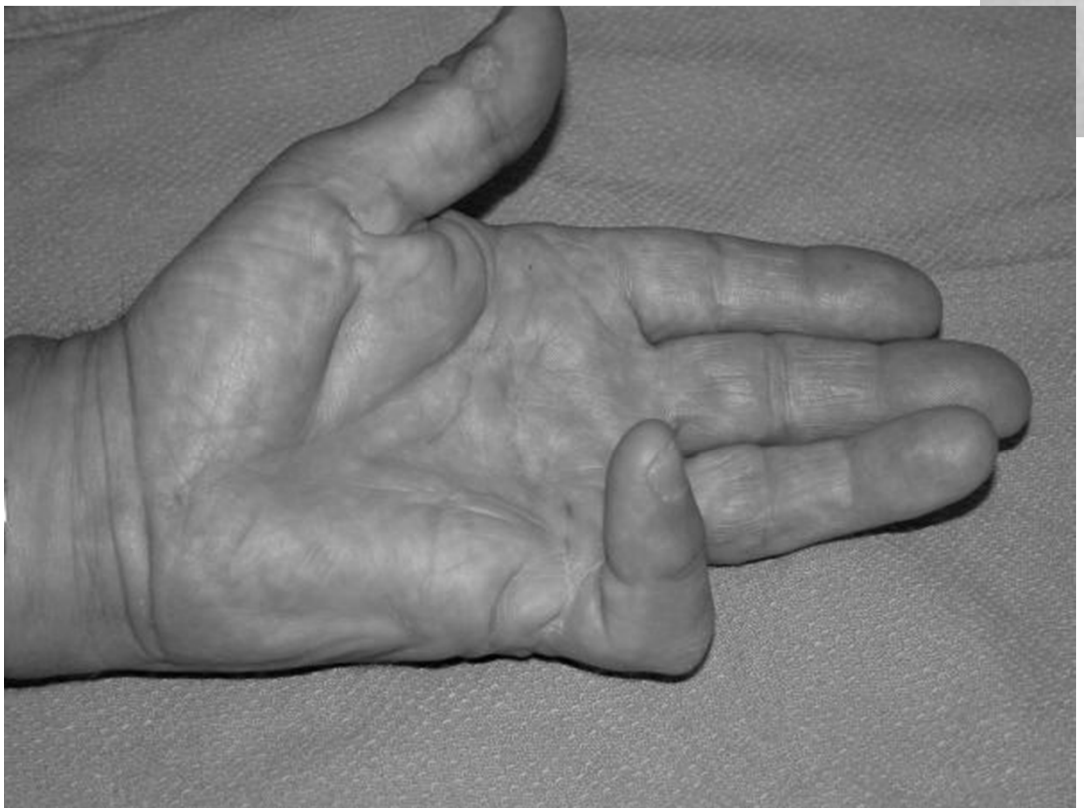


Palmar erythema









Dupuytren's contracture

*Ascites is usually manifested by abdominal distension .

*Edema of the legs is frequently associated.

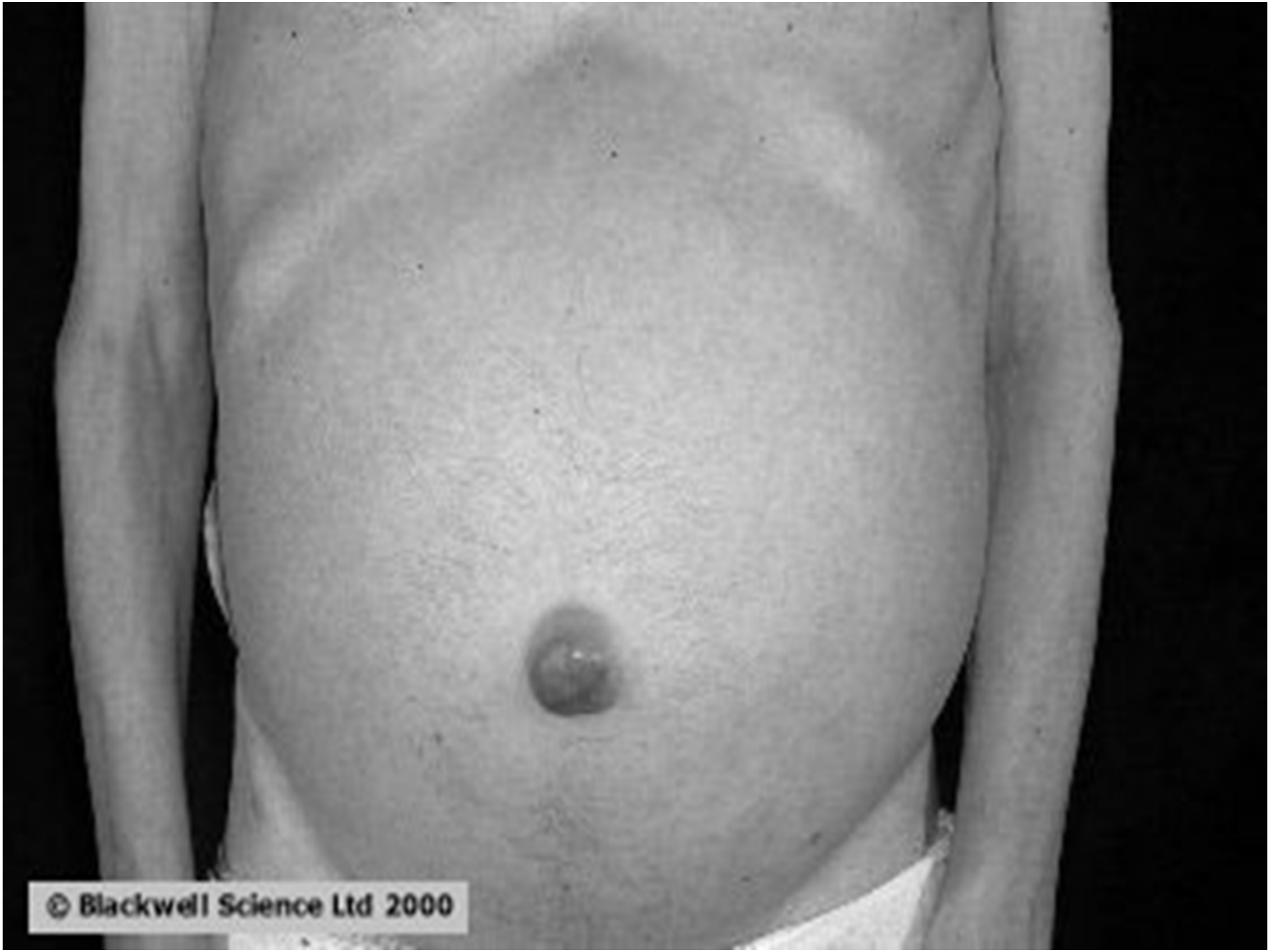
*The liver may be enlarged or shrunken, with a firm regular edge.

*The spleen may be palpable.

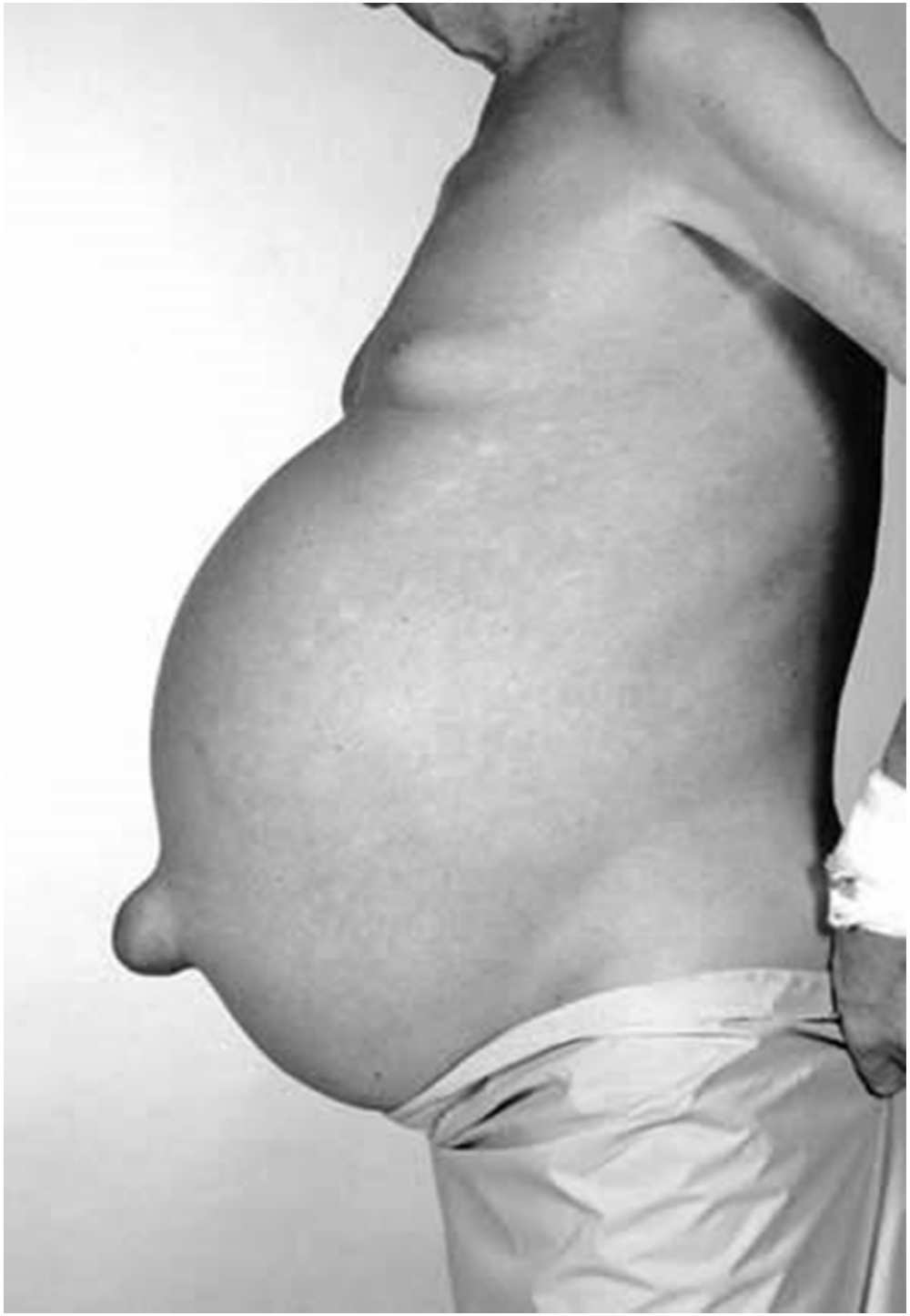
*Features of portal hypertension

* Ascites
* Splenomegaly +/- hyperslenism
* Caput medusae
* Evidence of hyperdynamic circulation (e.g., resting tachycardia)
* opening of portosystemic collaterals

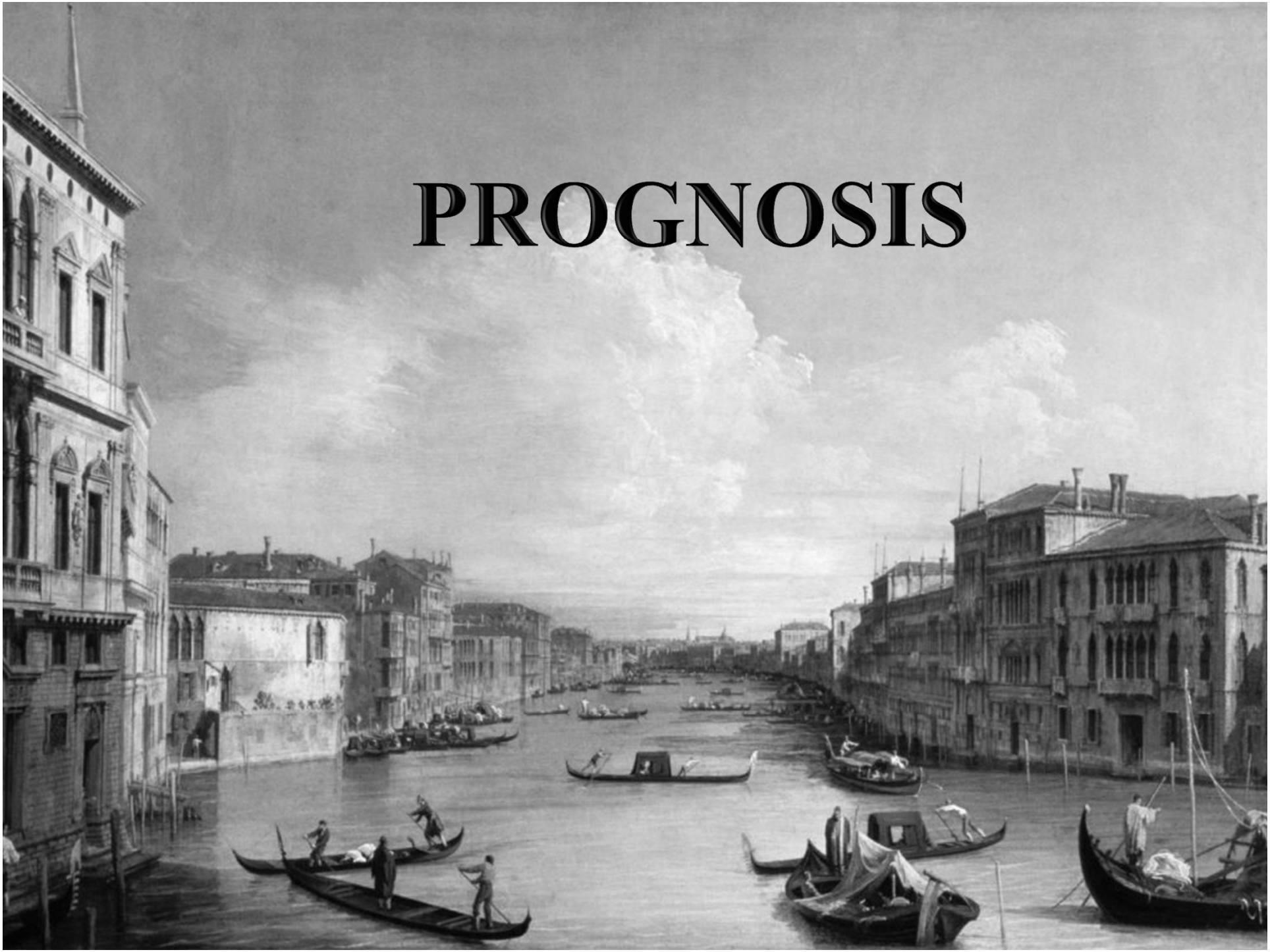
(Varices, Portal Hypertensive Gastroenteropathy)



- Jaundice
- Muscle wasting
- Gynaecomastia
- loss of axillary and pubic hair



PROGNOSIS



* *Assessment of the severity of cirrhosis*
Child- Turcotte-Pugh (CTP) scoring system

	Numerical score		
	1	2	3
Parameter			
Ascites	None	Slight	Moderate/severe
Encephalopathy	None	Slight/moderate	Moderate/severe
Bilirubin (mg/dL)	<2.0	2–3	>3.0
Albumin (mg/L)	>3.5	2.8–3.5	<2.8
Prothrombin time (sec increased)	1–3	4–6	>6.0
Total numerical score	**Child Pugh class**		
5–6	A		
7–9	B		
10–15	C		

*1. Patients with compensated cirrhosis may have a relatively long life expectancy if they do not exhibit evidence of decompensation; estimated 10-year survival in compensated patients is 47%, but estimated 5-year survival is only 16% when decompensation occurs.

*2. In patients with cirrhosis and varices who have not yet had their first variceal hemorrhage, the risk of bleeding from varices can be predicted based on a scoring system that incorporates the CTP classification, the size of varices, and certain endoscopic stigmata such as red wale markings and cherry-red spots on varices

*3. In cirrhotic patients, the risk of general anesthesia and operative mortality also correlates with the CTP classification.

*Laboratory investigations :

*Hematology :

*Anemia :

*There is usually a mild normocytic , normochromic anemia; it is occasionally macrocytic. Gastrointestinal bleeding leads to hypochromic anemia.

*Leucopenia.

*Thrombocytopenia.

*The prothrombin time is prolonged and does not return to normal with vitamin K therapy.

*Serum biochemical changes :

***a. Tests of hepatocellular injury**

*Aminotransferases

(aspartate aminotransferase [AST] and alanine aminotransferase [ALT]): most forms of chronic hepatitis other than alcohol have an AST/ALT ratio of less than 1; however, as chronic hepatitis progresses to cirrhosis, the ratio of AST/ALT may reverse.

*Serum biochemical changes :

***b. Tests of cholestasis**

*Alkaline phosphatase

* Serum bilirubin (conjugated and unconjugated)

* Gamma glutamyltranspeptidase (GGTP)

* 5’-Nucleotidase

***C.Tests of synthetic function**

*n Serum albumin

*n Prothrombin time

*d. Special tests to aid in diagnosis

*Viral hepatitis serology (HCVAb, HBsAg, HBcAb)

* PCR techniques for detecting viral RNA or DNA

* Serum iron, total iron binding capacity (TIBC), ferritin, genetic testing for the *HFE* gene mutation (hemochromatosis).

* Ceruloplasmin, serum and urinary copper (Wilson disease)

* Alpha-1 antitrypsin level and protease inhibitor type

*d. Special tests to aid in diagnosis

*Serum immunoglobulins (autoimmune hepatitis)

*Autoantibodies: antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), anti–liver kidney microsomal antibodies (LKM), anti–smooth muscle antibodies (SMA) (autoimmune hepatitis, primary biliary cirrhosis)

*e. Screening test for hepatocellular carcinoma: serum alpha fetoprotein

*Abdominal ultrasound :

*Mixed coarse echopattern, irregular hepatic outline,early hepatomegaly, late shrunken.

*Dilated portal vein.

*Enlarged spleen.

*Ascites.

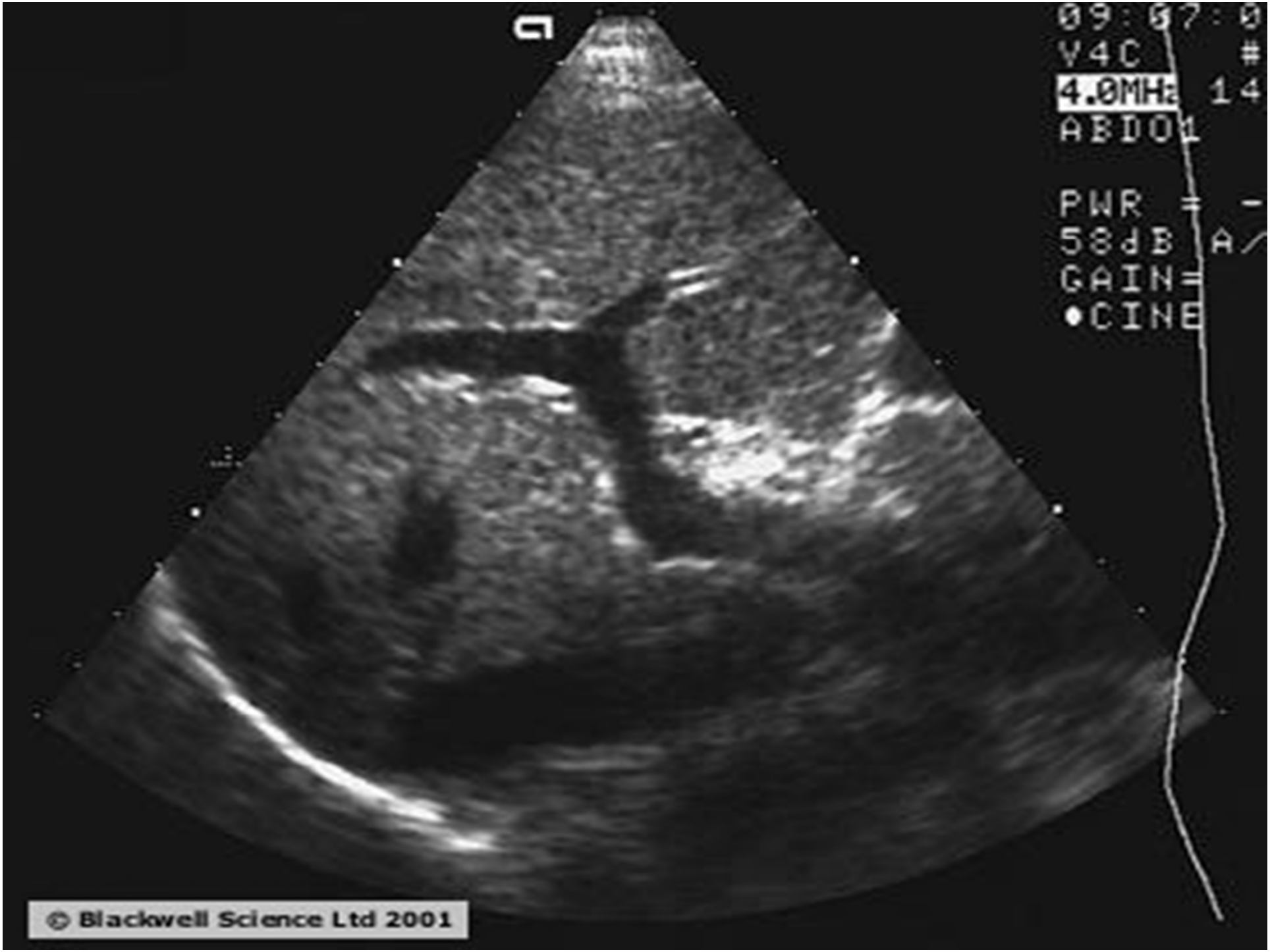
*Noninvasive, relatively inexpensive

* Can easily biliary dilatation

* Screening test for primary hepatocellular carcinoma

*Duplex Doppler ultrasonography can further assess hepatic and portal vein

*patency



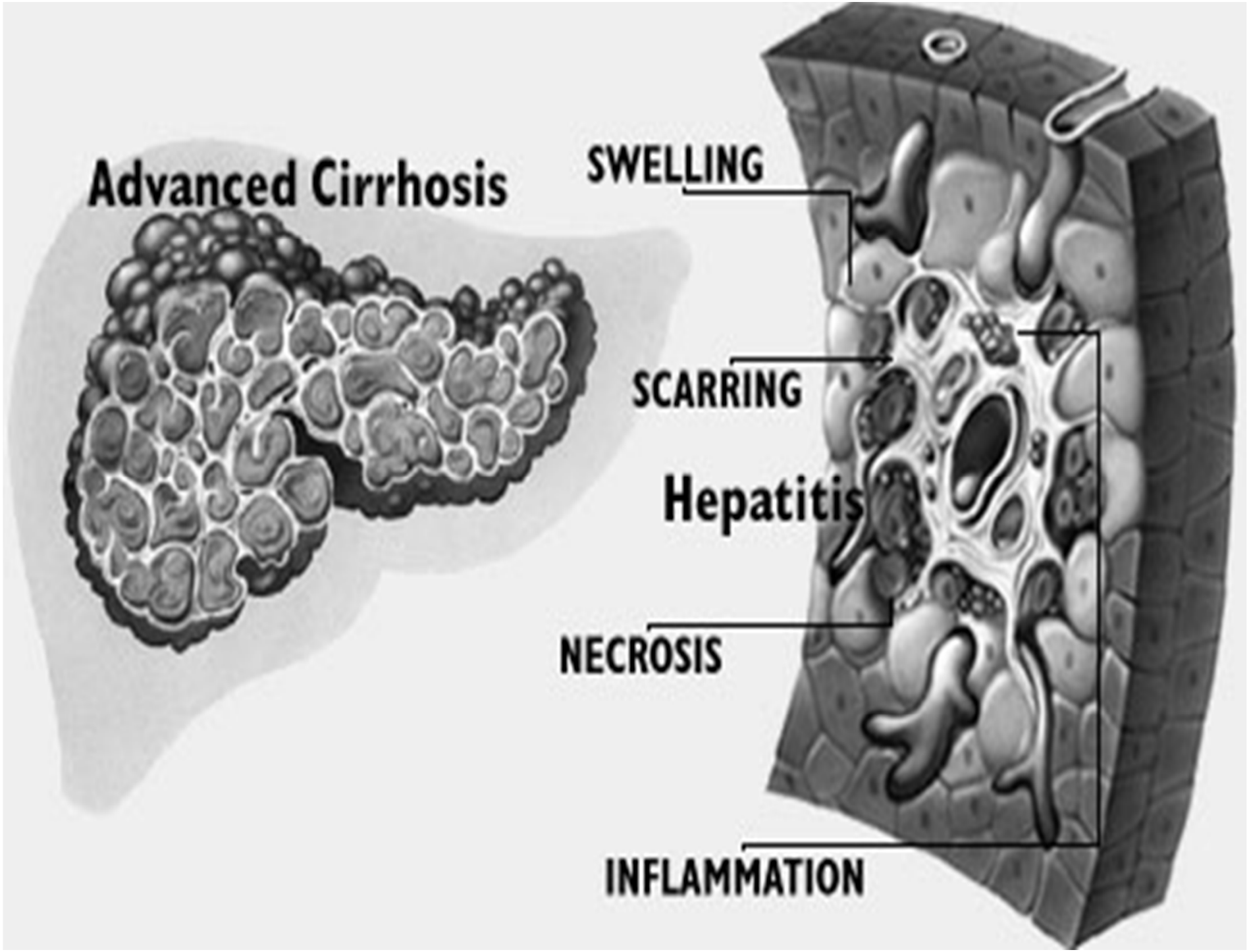
*Liver biopsy :

*Needle liver biopsy: may give a clue to the etiology and inflammatory activity.

*If there are contraindications, such as ascites or a coagulation defect , the transjugular approach should be used.

*Reticulin and collagen stains are essential for the demonstration of fibrosis around the nodules.

Liver biopsy is performed in selected patients with chronic liver disease when the clinical, biochemical, and radiologic data are not definitive for cirrhosis.


Advanced Cirrhosis
SWELLING
SCARRING
Hepatitis
NECROSIS
INFLAMMATION

Specific histologic methods

- Immunohistochemistry (e.g., hepatitis B virus)
- Polymerase chain reaction (PCR) techniques (e.g., hepatitis C virus)
- Quantitative copper measurement (Wilson disease)
- n Periodic acid–Schiff (PAS)–positive, diastase-resistant globules (alpha-1 antitrypsin deficiency)
- Quantitative iron measurement (hemochromatosis)

ALTERNATIVE TESTS

IMAGING	BIOMARKERS
US, TC, MNR, Elastography (phisical parameter related to liver elasticity)	Serum parameters directly/indirectly related to fibrosis and/or fibrogenesis

DEVELOPED TO PREDICT HISTOLOGICAL STAGE: SURROGATES OF BIOPSY

MG

BIOMARKERS

Better performance in discriminating the extreme stages and in diagnosing cirrhosis

OVERALL PERFORMANCE:

No/mild fibrosis *vs* "significant" fibrosis:
AUC = 0.77 (median)

No-cirrhosis *vs* cirrhosis:
AUC = 0.87 (median)

MG

*Complications of Cirrhosis:

*Gastro-esophageal variceal bleeding or bleeding from portal H. gastropathy .

*Hepatic (porto-systemic) encephalopathy, Peripheral neuropathy and asterixis.

*Ascites, spontaneous bacterial peritonitis, and the hepatorenal syndrome .

*Hepatocellular carcinoma.

*Cardiopulmonary complications.

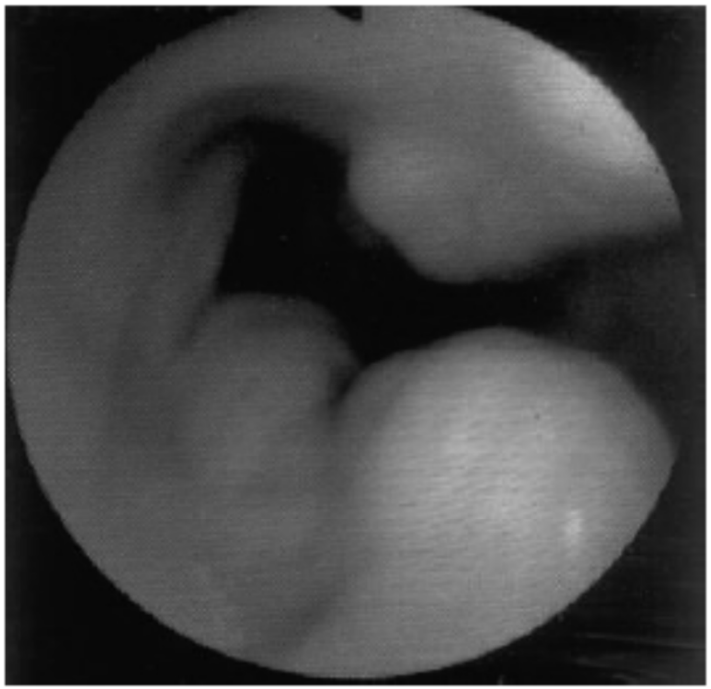
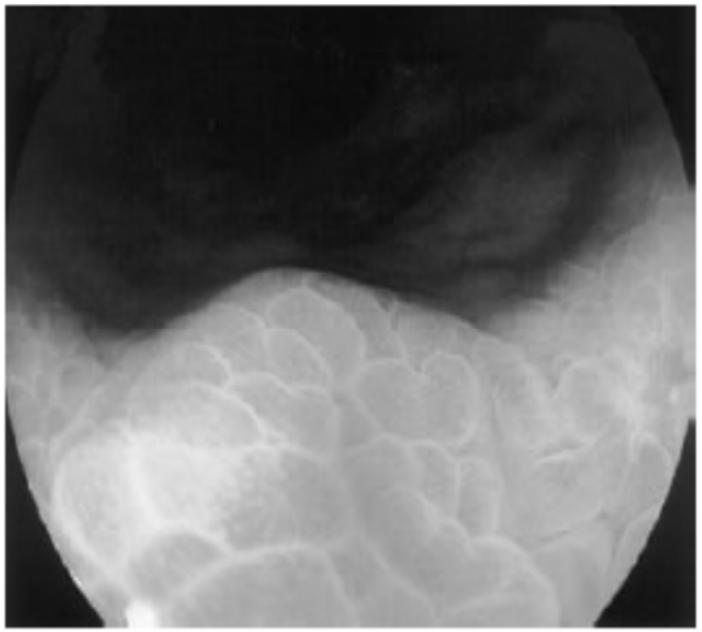
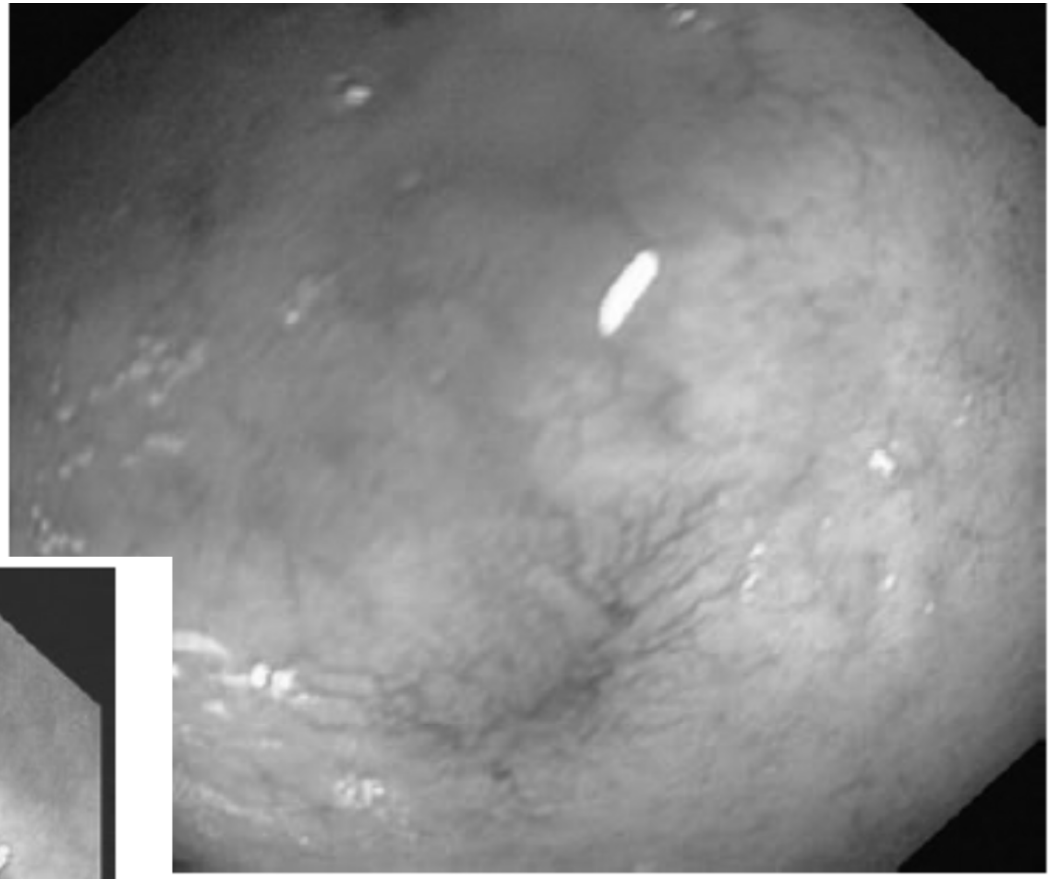


Fig. 80.4 Third degree esophageal varices, protruding into the esophageal lumen without contacting each other



0.10 Portal hypertensive gastropathy. The mucosa has a
ar pattern reminiscent of a snakeskin



2 Spider angioma of rectal mucosa in a patient with

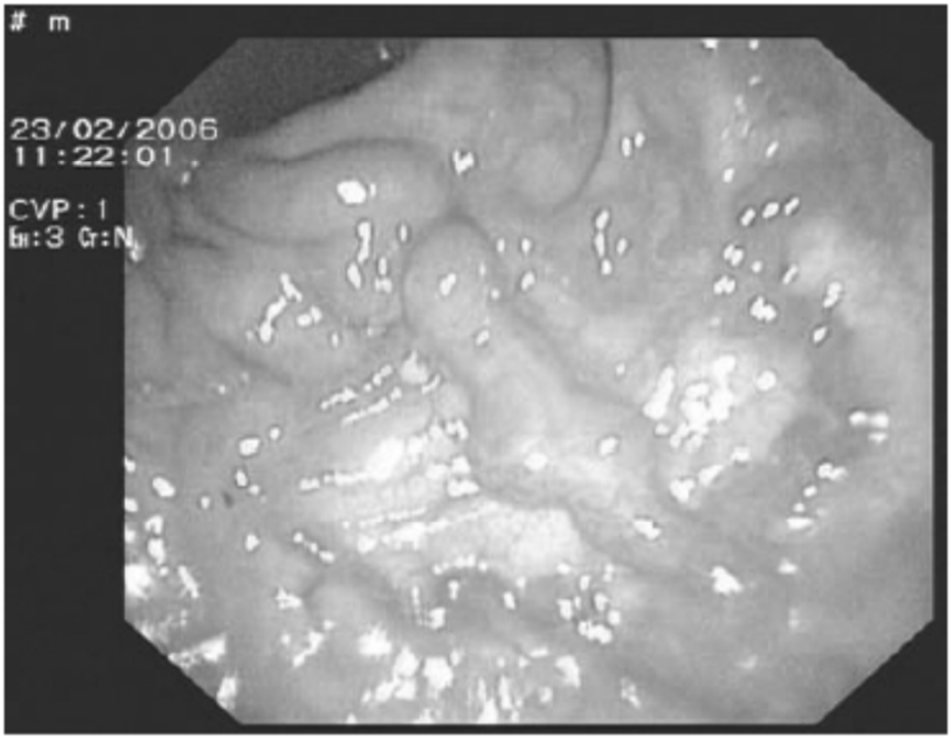


Fig. 80.11 Rectal v\arices in a patient with cirrhosis and portal hypertension

* ***Cardiovascular Complications of Cirrhosis:***

*a. Hyperdynamic Circulation

*denotes cardiovascular alterations in patients with liver cirrhosis that are characterized by a decrease in systemic peripheral vascular resistance, peripheral vasodilatation, low arterial blood pressure and a compensatory increase of cardiac output per minute in the presence of a low A-V oxygen gradient. These changes only rarely lead to heart insufficiency.

* ***Pulmonary Complications of Cirrhosis:***

*a. Decreased oxygen saturation

*b. Altered ventilation–perfusion relationships

*c. Portopulmonary hypertension

*d. Hyperventilation

*e. Reduced pulmonary diffusion capacity

* ***Pulmonary Complications of Cirrhosis:***

*f. Hepatic hydrothorax

- Accumulation of fluid within the pleural space in association with cirrhosis and in the absence of primary pulmonary or cardiac disease
- Usually right-sided (70%)
- Typically associated with clinically apparent ascites, but can be found in patients without ascites

* ***Pulmonary Complications of Cirrhosis:***

*g. **Hepatopulmonary syndrome**

* n Triad of liver disease, an increased alveolar–arterial gradient while breathing room air, and evidence for intrapulmonary vascular dilatations

* Wide reported range of prevalence in cirrhotic patients from approximately 5% to 50%

* ***Pulmonary Complications of Cirrhosis:***

*g. **Hepatopulmonary syndrome**

- Characterized by dyspnea, platypnea, orthodeoxia, digital clubbing, and severe hypoxemia (PO_2 less than 80 mm Hg, and often less than 60 mm Hg)
- Intrapulmonary shunting demonstrated by contrast-enhanced (“bubble”) echocardiography or technetium-99m macroaggregated albumin scanning; pulmonary arteriography rarely required

* **Endocrinologic complications**

*a. **Hypogonadism**

* Male patients: loss of libido, testicular atrophy, impotence, decreased amounts of testosterone

*Female patients: infertility, dysmenorrhea, loss of secondary sexual characteristics

*__Endocrinologic complications:__

*b. **Feminization** (acquisition of estrogen-induced characteristics)

* Spider telangiectasias

* Palmar erythema

* Gynecomastia

* Changes in body hair patterns

*c. Disturbed glucose tolerance, overt diabetes mellitus and hypoglycemia may be observed in patients with liver cirrhosis

Hepatic Osteodystrophy

*Definition:

*The term hepatic osteodystrophy (HO, hepatic osteopathy,hepatic osteopenia) denotes the metabolic bone disease that occurs in patients with chronic liver disease. HO encompasses both osteoporosis and osteomalacia, with the former largely prevailing.

Hepatic Osteodystrophy

*Overall reduced bone formation rate due to impaired osteobast function is the leading pathogenetic mechanism, rather than increased osteoclastic bone degradation.

*Hypogonadism often present in cirrhotic patients is an important promoting factor.

Hepatic Osteodystrophy

*Despite altered vitamin D and calcium metabolism (e.g. diminished intestinal absorption of fat soluble vitamins; 25-hydroxylation of cholecalciferol remains intact even in advanced stages of cirrhosis), bone mineralization appears unaffected even in advanced cholestatic liver disease


TREATMENT

The major goals of treating patients with cirrhosis include:

- Slowing or reversing the progression of liver disease.
- Preventing superimposed insults to the liver.
- Preventing and treating the complication.
- Determining the appropriateness and optimal timing for liver transplantation

*1. Specific treatments are available in certain instances:

* Phlebotomy for hemochromatosis
* d-Penicillamine for Wilson disease
* Avoidance of alcohol for alcohol-induced cirrhosis
* Combination of peginterferon alfa and ribavirin for chronic hepatitis C
* Lamivudine, adefovir, entecavir, telbivudine or tenofovir for chronic hepatitis B (interferon usually avoided in cirrhosis caused by chronic hepatitis B)
* Corticosteroids for autoimmune hepatitis
* Ursodeoxycholic acid for primary biliary cirrhosis

*2. In most cases, management focuses on the treatment of complications

that arise in the setting of cirrhosis (e.g., variceal hemorrhage, hepatic encephalopathy, ascites, and spontaneous bacterial peritonitis).

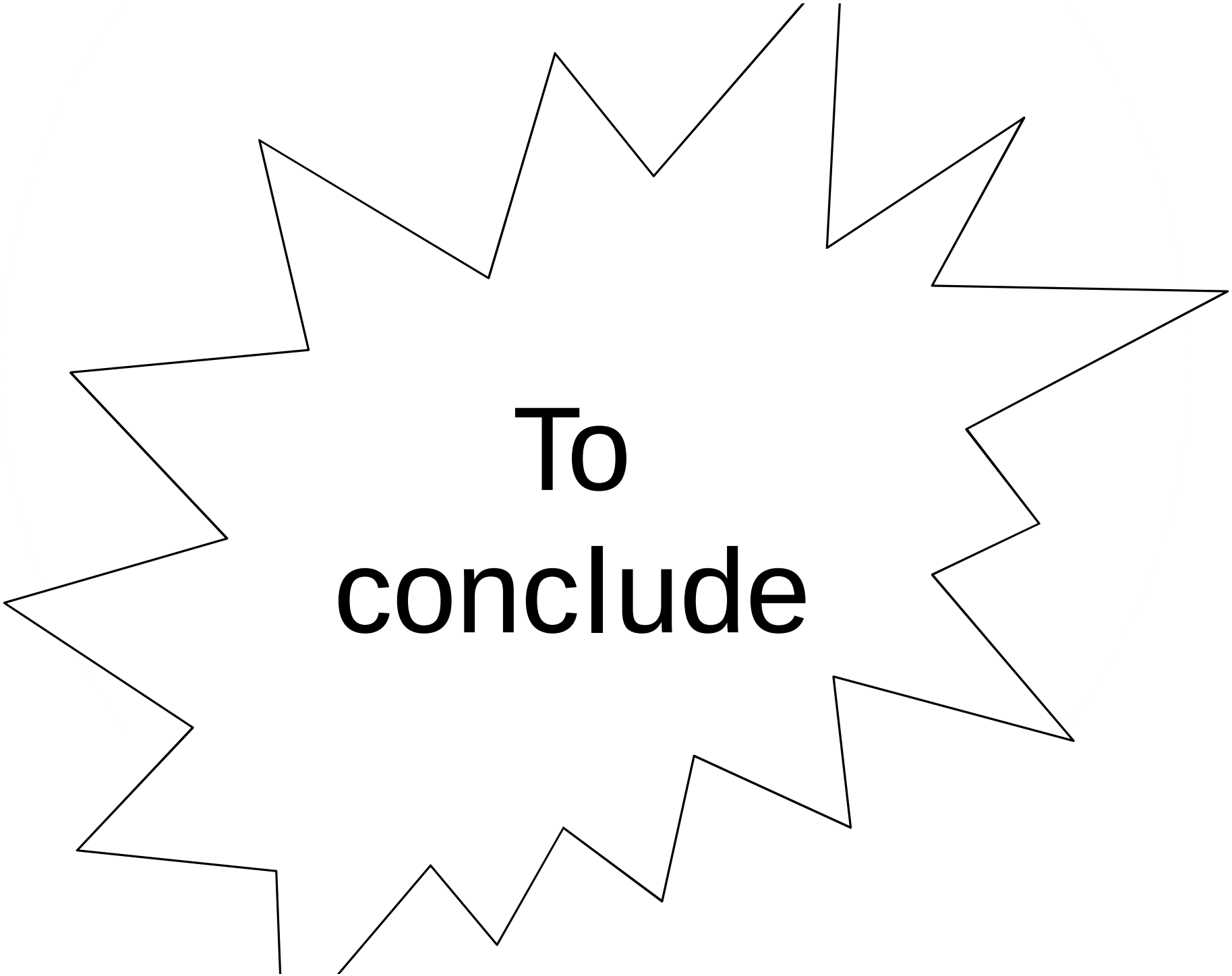
3. Surveillance for hepatocellular carcinoma with serial ultrasound examinations and serum alpha fetoprotein measurements at frequent intervals (e.g., every 6 months) is generally recommended in patients with cirrhosis.

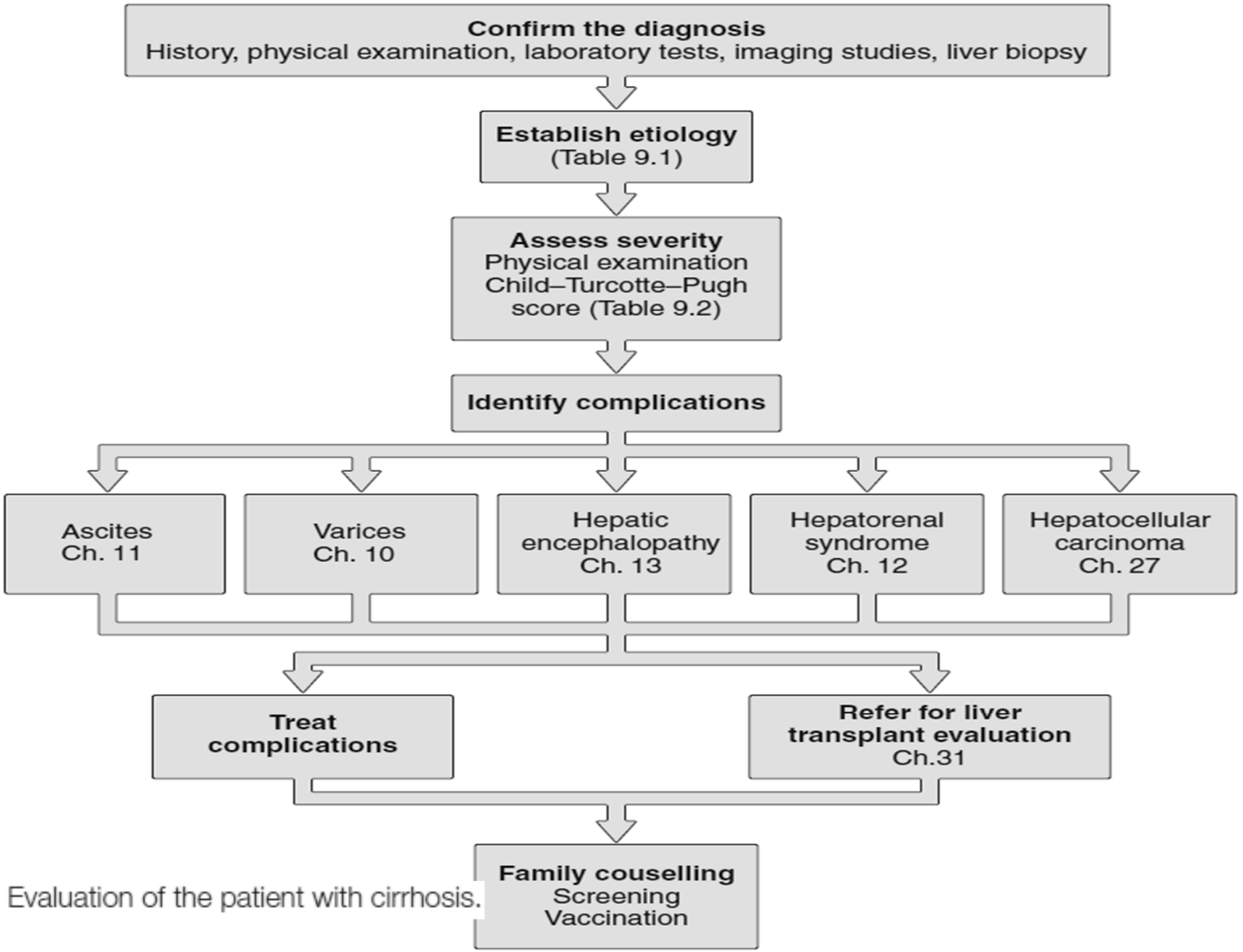
*4. Vaccination of cirrhotic patients against hepatitis A and B

is recommended if patients lack serologic evidence of immunity.

5. Cirrhotic patients should be advised to avoid alcohol and other hepatotoxins.

6. In end-stage cirrhosis, liver transplantation can be a lifesaving procedure if the patient is an appropriate candidate


To
conclude



Evaluation of the patient with cirrhosis.

" اللهم ارزقنی حبك وحب من یحبك و حب كل عمل یقربنی الی حبك"